CHAPTER XXIX

YAWS; FRAMBOESIA TROPICA

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Definition

A prerequisite to intelligent discussion of any disease is a limiting definition to serve as a framework upon which to build the story of its natural history Yaws is a chronic relapsing infectious disease of man caused by a tenuous spiral organism of the genus *Treponema*, it is characterized by hypertrophic granulomatous or ulcerative destructive lesions of the skin by destructive and hypertrophic changes in the bones by positive reactions of the serum to various serologic tests using mammalian tissue lipoids as antigens and *by a favorable response to certain* arsenical and bismuth preparations and to the antibiotic penicillin In its natural evolution in man there is usually an early period beginning with a single initial lesion the primary or mother yaw followed by a generalized eruption often before the first lesion has healed and a late stage with an intervening period of latency

Yaws is a common condition throughout the tropical world especially in damp forested areas and sporadic cases are reported from other regions Because of its wide distribution like syphilis it has been given many names names which have varied with time place and language Yaws is the common English name framboesia tropica the raspberry of the tropics is that most universally used in the French Islands it is called pian in Spanish territory bubas in Portuguese countries bouba or boubas in India and Ceylon parangi in the Pacific Islands tonga or tona or some similar variant and in the Dutch East Indies Ambovna pocks was once used Hermans[1] cited fifty names in an incomplete list of synonyms for framboesia

From our basic definition of yaws as a condition caused by a treponema with a fairly uniform pattern of evolution in the human host one may not distinguish it from syphilis bejel of the Arabs pinta of South and Central America irkintja of the Australian hinterland or from tribal syphilis of North Africa All conform to one basic definition all are closely related conditions Because some clinical manifestations of infection are commoner in one than in the others it is given a different name but all are generically the same Hudson who stated that they are merely different clinical syndromes distinguished clearly between a disease entity the character of which *has the quality of stability its* course is definitely predictable its pathology remains true to certain fundamental tissue changes its serology and immunology follow definite laws its therapy is consistently effective and a clinical entity syndrome or pattern which is a group of signs and symptoms which may

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Yaws is a common condition throughout the tropical world, especially in damp forested areas, and sporadic cases are reported from other regions. Because of its wide distribution, like syphilis, it has been given many names, names which have varied with time, place and language. Yaws is the common English name; *framboesia tropica*, the raspberry of the tropics, is that most universally used; in the French Islands it is called pian; in Spanish territory, bubas; in Portuguese countries, bouba or boubas; in India and Ceylon, parangi; in the Pacific Islands, tonga or tona or some similar variant; and in the Dutch East Indies Amboyna pocks was once used. Hermans[1] cited fifty names in an incomplete list of synonyms for framboesia.

From our basic definition of yaws as a condition caused by a treponema with a fairly uniform pattern of evolution in the human host, one may not distinguish it from syphilis, bejel of the Arabs, pinta of South and Central America, irkintja of the Australian hinterland or from tribal syphilis of North Africa. All conform to one basic definition; all are closely related conditions. Because some clinical manifestations of infection are commoner in one than in the others, it is given a different name, but all are generically the same. Hudson[2] who stated that they are merely different clinical syndromes, distinguished clearly between a disease entity, the character of which has the quality of stability: its course is definitely predictable, its pathology remains true to certain fundamental tissue changes, its serology and immunology follow definite laws, its therapy is consistently effective; and a clinical entity, syndrome or pattern, which is a group of signs and symptoms which may

occur together helping stability and which, because of its dependence upon extraneous factors is fundamentally fluid in character. There may be transitional patterns of disease which present certain characteristics of clinical entities far to the left and far to the right, characteristics not common to all.

Thus far our definition of yaws does not permit a differentiation from other clinical patterns resulting from infection with treponemes because it includes factors common to all. We must go much farther into a comparison of similarities and differences which exist in order to understand yaws as a clinical entity. One thing should be emphasized at the outset. Yaws framboesia tropica is recognized only when and where one type of skin lesion develops with or without other types of lesions and that is the hypertrophic, elevated papule which has a granular raspberry like surface which usually is covered with a yellowish-gray crust. Such lesions may be absent from one or many cases in a group infected with treponemes but they must be present in some, or the condition is called by another name such as syphilis bejel or pinta. It is well known that hypertrophic papular framboesiform lesions may appear in syphilis of the temperate zone but such lesions usually occur in few of the many cases of syphilis encountered, while in yaws they are the rule rather than the exception.

Historical Background

The time and place where the ancestors of present day *Treponema pertenue* first parasitized man the type of lesions first produced and their subsequent evolution are unknown. From available records the present pattern of disease with raised crusted papules ulcerations and bony swellings appears to have been the same for the past three or four centuries but beyond that descriptions are vague indistinct and confused. One sees only a blurred outline of skin eruptions ulcerations and destructive processes called by different names some associated with sexual taint some set apart as responding favorably to mercury or to such medieval escharotics as copper sulfate or copper acetate[2]

It is not surprising that confusion results from exploration into accounts of disease in the ages before printing speeded the exchange of ideas before the bacterial etiology of infectious disease was defined and before serological tests and histopathological distinctions were elaborated. Even with the precise diagnostic methods available to us

today a differential diagnosis between syphilis and leprosy leprosy and sarcoid or yaws and syphilis may be difficult or impossible

That treponematous diseases are very ancient seems to be true beyond all doubt but it is impossible to determine what clinical patterns predominated in Africa Asia or in the New World of Columbus and when the various types developed whether mucous patches aortic involvement and invasion of nerve tissue were part of the pattern or whether raspberry like papules and extensive ulcerations of the skin with great deformities of the bones were the obvious manifestations in the apparent absence of the former Here and there one finds descriptions of disease which are clear enough to permit a tentative diagnosis between tropical yaws and temperate syphilis

Hamlin[7] in his article on the geography of treponematosis distinguished between yaws, a rural tropical type, syphilis a more urban form of practically world wide occurrence and a disease of many names epidemic syphilis commonly not associated with venereal transmission He believed that the disease now known as yaws was undoubtedly indigenous to remote parts of Africa Australia, Melanesia and South America long before any recorded contact was established with European areas Africa was the original homeland of treponematosis according to Hamlin from which it spread to Asia the Pacific Islands even to the American Continent in prehistoric times gradually changing assuming slightly different forms as factors of environment and host varied with the resulting survival of mutant strains of treponemes He stated that the evolutionary affinity of yaws and syphilis as shown by clinical pathological and immunological comparison is further emphasized by their geographic relationship But in spite of his conviction that yaws (treponematosis) spread widely from Africa to Asia and to the Pacific area thousands of years ago he subscribed to the belief that syphilis suddenly emerged in Europe in Columbian times probably as a result of importation of cases of treponematosis acquired by members of Columbus crew from native women in the New World

Hudson believed that as long as treponematosis remained in moist tropical zones it retained its character as a childhood disease with florid skin eruptions but that as it spread to dry arid regions, to temperate and cold climates its character was changed The early eruptions became less florid the lesions tending to become grouped about the warm moist parts of the body particularly about the mouth anus and vulva and mucous membrane vascular and nerve involvement began to ap

pear. Granting that such an evolution took place, it is easy to explain why transmission through casual bodily contact in childhood or by insects became more difficult and tended more and more to result from sexual contact and hence the age of infection advanced from childhood to adult life. However in many areas because of lack of cleanliness and because of crowding in sleeping and living quarters the transmission of spirochetes by direct skin contact and probably by contaminated articles continued to play an important role.

The eminent medical historian Sudhoff after careful study of original documents of pre and post Columbian times came to the belief that a disease later to be known as syphilis had existed for many centuries before the Renaissance in Europe and Arabia but that it was confused with other conditions such as leprosy. As a result of alchemistic studies of the Occident mercury for inunctions began to be used in the twelfth century and in the course of several generations the practitioner learned to set apart from the great number of skin diseases treated with mercury a group which was favorably influenced by inunctions. Because of its failure to respond to inunctions leprosy was set apart from other ulcerative and destructive skin conditions which did respond. In the fourteenth century this knowledge penetrated to Northern Italy and Southern France where such names as scabies grossa, variola grossa' or grosse verole were in common use[4]

Holcomb who called the theory of the American origin of syphilis the ancient myth thought that treponematous patterns of disease existed in the early days of the Greeks and Romans and had spread to Western and Southwestern Europe probably centuries before the New World was first seen by Europeans[5] There was a disease the Greeks called lichens which was described by Pliny in the first century of the Christian era and called mentagra. Pliny's description of mentagra was well known and had long been confused with or identified as syphilis by the early writers. Holcomb quoted Pliny's Book 26 on mentagra

Even though without pain and without destruction of life yet there were diseases so loathsome that any kind of death would be preferable to them. The most grave of these was called the lichens from its Greek name. Whereas for the most part it became visible on the chin by way of a joke at first playfully it soon became generally though improperly known as mentagra. The disease takes possession of the whole face spreading from within excepting only the eyes the foulness to speak the truth descending downward to the neck breasts hands covering the hands with a filthy scurf. The lues was unknown to

the ancients and even in the time of our fathers It first spread into Italy the middle of the reign of Tiberius Claudius Caesar

According to Holcomb bois the latin word for buvas or bubas was an ancient disease in Spain a syphilis like eruption known for over a thousand years He stated that Pliny the Elder (3 79 A D), served as procurator in Gallia Narbonensis and Hispania Terraconensis and he incorporated in his Natural History several remedies for the Bois including remedies for lichens with mouth ulcers carbuncles and ulcers of the genitalia Bois was described as a malady which appeared in the form of red papules about the body After the invention of printing the first book on the buvas in the Spanish tongue was a poem by Francisco Villalobos published at Salamanca in 1498 In the second part of the book Villalobos described the opinions of the time and quoted as historical material an account by the Bishop of Seville (570 636 A D) of the ancient impetigo 'The dry scabies It bursts forth upon the body as an eruption of rough and circular form '

Chambers[6] also thought that yaws was of ancient lineage older than syphilis and although he stated that they are two distinct diseases he believed that syphilis is a biological development of yaws consequent on infection in a completely non immune race living under different environmental conditions He is one of the protagonists of the theory of the American origin of syphilis and arrived at this conclusion through some rather involved reasoning For example syphilis existed in America before 149 while yaws did not yaws was carried to the Western Hemisphere and introduced for the first time by slaves from West Africa hence Columbus men could not have contracted yaws there but he stated that Oviedo y Valdez, the Spanish historian who was in Mexico in 1525 gave the first description of yaws under the name of bubas However if syphilis is a biological variant of yaws then yaws must have existed in Mexico before 149 or at least it could not have been introduced first by West Africans who were not brought to Mexico in any great numbers until after the first decade of the 16th century And if this transition took place in Mexico before or after 149 why did it not take place also in Europe in the fifteenth century or earlier? The West African slave trade with Europe began as early as 1443 according to Bandinell[7] and subsequently many hundred West Africans were taken to Portugal annually for many years It is almost certain that some if not most of the negro slaves were infected with yaws because they were taken from the old Guinea Coast where yaws

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These types may be recognized as more or less distinct when seen in the mass although individual cases picked from the various groups may appear identical as to morphology of lesions and spirochetes histologic changes serologic reactions and response to treatment Treponematosis may be thought of as a spectrum of patterns of reaction to invading spirochetes with primitive juvenile florid yaws a disease affecting mainly skin and bone tissues at one extreme with tribal syphilis bejel and pinta at the center less florid more often acquired in adult life than yaws with mucous membrane vascular and nerve involvement becoming apparent and at the extreme right civilized adult syphilis nearly always transmitted by sexual contact a pattern with relatively slight skin eruptions with frequent involvement of mucosae, blood vessels and nervous system But the spectrum is not constant the bands overlap patterns may be found out of place and a right type may be found in a group to the left of center or a left type may be found far to the right

The historical evolution of our knowledge of the yaws syndrome cannot be traced with any clarity or certainty more than a few hundred years possibly as far back as the early years of the sixteenth century Even since that time the outlines are all too often hazy and obscured confused with other conditions some unrelated to spirochetes and it is only since the demonstration of the causal relationship of the treponemata to syphilis yaws and other patterns and the development of serologic tests and histologic technics in diagnosis that a clear picture has begun to emerge The earlier writings of the last few hundred years reveal numerous accounts of skin eruptions called by various names such as yaws framboesia bubas parangi etc from tropical America Africa or the Pacific Islands The description of the florid type of skin lesions the disease usually appearing in childhood and as a community infection leaves little doubt that what we now know as yaws was being described but clear details are for the most part lacking

It is not known who wrote the first description of framboesia Chambers[6] believed that Oviedo the Spanish historian was the first to describe the disease Oviedo or Gonzalo Fernandez Oviedo y Valdes who was born in Spain in 1478 was named Inspector of Gold Foundries of the American Colonies and came to the New World in 1513[11] In 1526 his book on the general and natural history of the Indies was published Various authors including Williams[12] Chambers[6] and Holcomb have used his accounts of bubas among the indigenes and among the

prevailed at the time when this part of the world was rediscovered by Portuguese explorers.

It is probable that we shall never know with absolute certainty when and where treponematous disease first afflicted man, and nor exactly what clinical patterns first developed, nor whether there was one or many areas of origin with subsequent world spread by way of migrations. The historical records are too vague and confused, often contradictory and made to fit a preconceived notion. William Cullen, whose "Synopsis of Medical Nosology" was published in 1793, stated "the moderns seldom turn over the books of the Ancients to procure the first knowledge of things but they are most often searched only that they may support their own discoveries and observations by such authority."[8]

Too often we have seen examples of twisting the words of others to support a conclusion already arrived at, although Butler in his introduction to Holcomb's book on the Haitian Myth stated that the author "has shown the folly of laying up mountains of half baked prejudice when a scholar digging into the records of the past can get at the truth of things without further complicating the literature."[9]

There is little doubt that treponematosis is indeed of very ancient lineage and has assumed many different patterns, of which yaws is but one, patterns probably conditioned at least in part by adaptation of mutant strains of the parasite to changing environmental conditions of the host, climatic and hygienic. It is more than likely that treponemata first parasitized man many thousands of years ago and that treponematosis had long been an established disease of men everywhere, including Europe, Africa and the Western Hemisphere, when Columbus made his voyages to the New World.

As Hudson has said, treponematosis is a constitutional disease caused by a versatile parasite which may change its angle of attack from a non-venereal disease of childhood to one of adult infection.[2] To go farther, it is probable that the angle of attack is constantly changing as factors of ecology are altered. There is probably no such thing as a "fixed" species or strain in the biological world, and Dubos[10] has indicated that bacterial mutation occurs with a certain regularity. Such mutant forms may be better or less well adapted to a parasitic life in the host, particularly in certain specific tissues of the host, depending upon many different factors including temperature, rate of metabolism and enzyme content. It is felt that as a result of mutations and adaptation to a changing host environment a number of clinical types of treponematosis have evolved.

Spanish terms used long before the Columbian era to designate an eruptive skin condition and Williams[12] who quotes from the writings of Las Casas Oviedo y Valdez and Ruiz Diaz de Isla Spanish cavalier of the early sixteenth century indicates that bubas was applied also to a skin disease found in the Indies which may have been yaws It is apparent that bubas probably referring to yaws was a common term elsewhere in the Spanish New World in the sixteenth century In 1587 a Portuguese colonist in a description of Brasil mentioned boubas in connection with its possible transmission by small flies[13]

According to Hermans' framboesia' was first used as a synonym for yaws in 1768 by Francisco Boissier de Sauvages in his work entitled Nosologica Medica The term was included in the synopsis of medical nosology written by William Cullen in about 1785 Syphilis and yaws were included in Class III Cachexies, Order III Depravations as follows

Genus LXXXV

A contagious disorder after impure venery and a disorder of the genitals ulcers of the tonsils of the skin especially of the margin of the hair corymbose papulae, going into crusts and crusty ulcers

The only species Venereal Syphilis

The Polonic syphilis S by no means belongs to this genus and we are not sufficiently acquainted with Indian syphilis S to put it down as a different species'

Genus LXXXIX Framboesia

Resemblance of mushrooms mulberry or raspberry fruit springing up in various parts of the skin

The varieties are Guinea Framboesia

American framboesia [8]

It will probably never be known with certainty whether yaws existed in the Western Hemisphere before the sixteenth century but it is certain from description of early colonists that the disease was widespread among the slaves and that the slave trade with Africa while it may not have been responsible for the original introduction of yaws was an important factor in its early epidemiology In a History of the Caribby Islands' rendered into English by Jonathan Davies and printed in London in 1666 there are recorded the observations of travelers of the previous hundred years or more In a section devoted to diseases of natives of the region it is stated The bad nourishment of Crabs and

Spanish conquerors to prove that syphilis or yaws existed in the New World at that time

Hermans[1], on the other hand, stated that in searching for the traces which framboesia has left on the history of disease and limiting the choice to those descriptions which were clear enough to avoid confusion with other conditions he was unable to go farther back than the beginning of the seventeenth century Jacobus Bontius, a Dutch physician who went to the Dutch Indies in 1627 left in his writings clear descriptions of framboesia, which was called the Indian hard swellings' or Amboyna pocks', which he encountered on the island of Amboyna in the Moluccas The following quotation from Bontius description is taken from Hermans monograph[1] 'In Amboyna and especially in the Molucca islands there is a general plague occurring frequently similar in its attacks to the Spanish pocks Yet it is different in so far as there is no Venus play in its etiology, it being usually propagated in the following way

'First, spots appear on the face and tophi or swellings on the arms and legs which are hard and scirrous from the beginning and occur as frequently over the whole body as warts and corns do on hands and feet in our own country, and if they ulcerate then a tough gum like substance is excreted which is so sharp and biting that deep ulcerations are excavated with hard horny and subverted edges

It is a filthy and loathsome disease and so similar to Spanish pocks but it is not so painful and does not so easily cause caries or death in the bone unless as the result of carelessness on the part of the medical practitioner

Hermans[1] quoted from another Dutch physician, Guglielmo Piso who accompanied the governor of Brasil to that country and whose work entitled de Medicina Brasiliensi , published in 1648 at Amsterdam included an account of the Venus disease or the pocks which was said to be prevalent and to arise not only from coitus but also from slight contagion a disease found not only in Africa and in the Indies but also affecting the Portugues and the Dutch who contract scirrous ulcers and stinking sores over the whole body it being a disease of this country called bubas' by the Spaniards and Brasilians (Piso quoted by Hermans[1])

Hermans apparently thought that Piso was the first to use the word bubas or bouba in speaking of framboesia but it is more than likely that the word had often been used in this connection long before Piso s time Holcomb[3] and others have shown clearly that buas or bubas are old

Spanish terms used long before the Columbian era to designate an eruptive skin condition and Williams[12] who quotes from the writings of Las Casas Oviedo y Valdez and Ruiz Diaz de Isla, Spanish cavalier of the early sixteenth century, indicates that bubas was applied also to a skin disease found in the Indies which may have been yaws It is apparent that 'bubas probably referring to yaws, was a common term elsewhere in the Spanish New World in the sixteenth century In 1587 a Portuguese colonist in a description of Brasil mentioned boubas in connection with its possible transmission by small flies[13]

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other insects on which they commonly feed, is the cause that they are most of them subject to a troublesome disease, which in their language they call pyans as the French call it a kind of Small Pox when those who are fallen into this disease eat of the Fram-tortoise they are immediately full of little risings inasmuch as these meats force the disease out"[14]

From the Island of Jamaica first colonized by the Spanish in the early 16th century, we have records of the presence of yaws for several hundred years In a list of the sick reported among the Spanish garrison on August 6, 1651, is the entry—'D Archivos Ronzel, tullido y con Bubas'[15] "A Discourse on the State of Health in the Island of Jamaica" by Thomas Trapham, M D published in 1679 on observations made many years earlier, refers frequently to the yaws not only among the native Indians but also among the negroes 'I find the old sower stocks of Venereal effects most plentiful among the animal Indians and the cursed posterity of naked Cham The first in the large tracts of the Americas the latter in the African deserts both which quarters of the world bring forth the monstrous yaws as a proper stock to engraft a new scion of disease, and that too fruitful the apples of Sodom and bitter fruits of Gomorrah of which the Europeans to their great cost have tasted under the new effect, called first the Neapolitan and then the French Disease, whose original being first the yaws, reduceth my discourse hither"[16]

Hans Sloan in his book on the natural history of the West Indies published in 1707 mentions yaws frequently He observed its occurrence in both Indians and negroes some of the latter 'not long from Guinea , and comments on its treatment by "fluxing by unction , he stated that it was thought to be contagious and to be communicated from one to another from black to whites and from parents to children and that there were few plantations without several of these diseased persons"[17]

William Hillary whose observations on the Island of Barbadoes were published in 1766, believed that yaws was a native of Africa and Arabia and was brought to America and its islands by Negroes from Africa He stated that yaws was a 'distemper' well known for many ages in Africa where it seldom failed to attack the Negroes most frequently young children His description of lesions of the skin the plantar surfaces and bones are clearly those of framboesia Hillary commented on the occurrence of the disease on slave ships coming from Africa and stated There is another vile custom which I must take notice of which the surgeons of the Guinea ships generally practice,

that is upon the first appearance of the yaws during the long voyage from Guinea they apply some strong repellants to them such as the juice of roasted limes mixed with the rust of iron and sulphur or gun powder—though they hereby render the skins clean for a short time, and then rub them with palm oil which makes them soft and look well, when they are imposed upon the Planters for sound healthful negroes—but in a few days or weeks the yaws break out again much worse than ever and are then very difficult to cure or sometimes incurable [18]

During the 18th and 19th centuries a number of other British authors mostly physicians published observations on the importance of yaws among the inhabitants of the West Indies especially among the negro slaves Bryan Edwards who lived in Jamaica subsequent to 1759 believed that the negroes brought yaws with them from Africa, and he observed that yaws was a disease very common among young children[19] John Williamson commented on the immense losses and the misery caused by yaws and stated that a yaws house should be erected on every property in Jamaica[a] Thomas Dancer noted the prevalence of yaws in Jamaica and gave an interesting account of thirty negroes on board a Guineaman who broke out with yaws during the voyage because of the presence of one yawey negro girl among them and who were radically and permanently cured by gentle mercurial salivation [21]

The practice of slavery began long before the Christian era and negro slaves were brought into Egypt Carthage and Rome in early dynastic times but the discovery of the New World gave a great impetus to the movement The slaves took with them wherever they went many of their diseases including yaws Because many parts of the New World soon came to be populated largely by natives of West Africa most of whom were undoubtedly infected with yaws in their homeland it is readily understood how the slave movement was a factor of tremendous importance in establishing the disease in the Americas Scott believes that when tropical medical history began framboesia already existed in many parts of the world including the Western Hemisphere but that the importation of infected slaves contributed much to its spread because of the continuous introduction of large numbers of new cases[3]

According to Bandinell s account of the slave trade West African negroes were first imported into Western Europe in 1442 when 10 slaves and some gold dust were brought back to Portugal The first West African slaves were brought to the New World in 1503 when a few were imported into Hispaniola (Haiti) to replace the Indians who

were not suited to hard work in the mines, and who died off or were killed so rapidly that the native population is said to have been reduced in a period of 15 years from a million to about sixty thousand[7] In the year 1511 Ferdinand the Catholic granted formal permission to import African slaves into Hispaniola but the trade in "black ivory" really became established as an important branch of commerce in 1517, when Charles V of Spain granted a patent to a Flemish gentleman of his court to import annually 4 000 Africans into Hispaniola, Puerto Rico, Cuba and Jamaica During the next several decades other European powers entered the lucrative trade The effect of the continued importation of negroes on the population complex may be appreciated from some of the early census figures Bryan Edwards stated that in Jamaica in 1655, when the British took over the Island from the Spaniards there were about 1,500 negroes and an equal number of whites, by 1744 there were 112,000 negroes and only 9 640 whites and by 1790 250,000 negroes and 30 000 whites[10] Scott estimated that there were in the North American Colonies in Virginia 12,000 negro slaves in 1700, and by 1760 there were 150 000 and in Carolina there were 22 000 in 1734 In the period from 1680 to 1786 he stated that 2,100,000 African slaves were brought to British American colonies

Slowly a feeling of revulsion against the traffic in humans grew in the white countries, laws were passed forbidding the traffic and by 1841 international slave trade was practically at an end although slavery continued to be practiced in many countries for several decades, the last great nation to abolish the practice being the United States

Other Treponematoses

To comprehend yaws in the individual or as a community disease it is necessary to have an understanding of some of the common and dissimilar features of other patterns of treponematosis which are described in many parts of the world They have many features in common including skin lesions bone involvement sometimes cardiovascular and nervous changes positive serologic tests a favorable response to the usual antisyphilitic drugs and the presence of treponemes in serum from early skin lesions These have been given a variety of names to set them apart from syphilis because it was felt that they differed from the usual evolutionary pattern of adult acquired "civilized" syphilis As mentioned previously pinta bejel tribal syphilis and

ard intpt are some of the names which have been applied to various patterns of infection with treponemes Some have used terms such as endemic, pandemic or primitive syphilis to indicate all syphilis-like disease except yaws found in primitive tribal peoples[21] It is interesting to note that some of these conditions are generally mutually exclusive in their geographic distribution for where yaws is common and endemic syphilis is seldom reported where syphilis is common yaws usually is uncommon Syphilis of the Euphrates Arabs is known by two local names 'bejel' and 'franghi' Bejel which is usually a childhood acquired non venereal disease is common among the nomadic Bedouin tribes but franghi or classical adult venereal syphilis is rare or absent Franghi on the other hand is common among the townspeople while bejel is absent[21] The distinctions between patterns of treponematous disease rest mainly upon epidemiological factors such as age and manner of infection and upon the preponderance of involvement of one or the other tissues of the body skin and bones cardiovascular system or nerve

Bejel

The form of syphilis called bejel is said to be so common among the nomad or farmer classes in Syria that almost every adult gives a history of having the disease when small[1,5] It is a childhood acquired disease not ordinarily associated with sex contact It usually manifests itself first as an eruption of the skin and mucous membranes without a primary sore being noticed The early skin lesions are macular or papular often hypertrophic and frequently circinate Mucous patches are common Plantar and palmar hyperkeratosis often with painful fissuring frequently occurs sometimes years after the original infection This type of lesion appears to become more severe in the cold wet season of the year A patchy depigmentation of the skin is seen frequently sometimes occurring in the extensive scars of early skin lesions or about the hands and feet in areas not obviously related to previous lesions Inflammatory or destructive lesions of the skin the long bones and nasopharynx are common late manifestations of bejel but lesions of the nervous or cardiovascular system occur seldom if at all Serum from early lesions contain abundant spirochetes with the morphology and motility characteristic of *T pallidum*[6,27,28] Serologic tests invariably become positive in the early stages and may remain so for many years in the absence of treatment[3,30] The lesions respond promptly

to treatment with the arsenicals or bismuth although small amounts of treatment are followed frequently by relapsing lesions and persistence of positive serologic tests[1]

Pinta

Pinta mal de pinto or carate as it is variously called, is a disease which was known for a long time as a skin disorder manifested by dyschromic changes such as areas of hypopigmentation or discoloration of varying shades of slate blue pink yellow or violet[2] Originally it was considered to be an involvement of the skin only and to be caused by various species of fungi However as serologic tests for syphilis became more widely used numerous workers noticed a correlation between the lesions of pinta and positive serologic tests It was soon found that the condition responded readily to arsenicals and to bismuth, and it was concluded that pinta was a treponematosis This was verified according to Holcomb on August 3 1938 when a treponeme was discovered in serum from active lesions in a case of pinta in Havana by Dr Grau Triana and Dr Alfonso Armenteros and two days later Dr Leon y Blanco demonstrated treponemes in fluid from enlarged lymph nodes These organisms were morphologically identical with *T pallidum* and with *T pertenue*[33] Pinta is found in many areas of the Western Hemisphere It has been reported from Colombia Venezuela Brazil Peru Ecuador and Argentina in South America and from parts of Mexico and Central America In the West Indies it has been reported from Cuba Haiti and the Dominican Republic[3] According to Varelo- and Avila there are approximately 270 000 people infected with pinta in Mexico and 500 000 in the rest of the Western Hemisphere especially in Colombia, Venezuela Ecuador and in Central America[34] Cases have been described elsewhere in the world and recently three cases were reported in the United States the diagnosis being based largely upon positive serologic tests and leucodermic spots[35]

Although the name pinta is an old one the first clear conception of the beginning and evolution of the disease was formulated in 1939 as a result of clinical observations and human inoculation experiments[36] All authors agree that the disease is acquired in the first two decades of life in the great majority of cases in the first decade in probably more than half Hence again we are dealing with a childhood-acquired treponematosis That it is transmissible directly from person to person has been amply demonstrated by the inoculation experiments of Leon y

Blanco and others who have inoculated human volunteers with material containing treponemes from generalized lesions of pinta The natural mode of transmission is not definitely understood but it is suspected that direct and indirect contact with infectious cases is largely responsible although various biting and sucking insects have been implicated In from 7 to 0 days after inoculation and at times longer a lesion appears at the site of injection This often is a small papule which gradually enlarges in size and becomes a flat scaling maculo-papular area frequently with scattered smaller lesions around the periphery

In the majority of cases the primary lesion develops on the legs or dorsum of the feet, less often on the hands or arms occasionally on the face buttocks and elsewhere Treponemes can be found in serum from primary lesions and from the satellite buboes It is said that the primary lesion never ulcerates and that serologic tests do not become positive before the appearance of the secondary eruption which develops 5 to 12 months after the primary lesion The secondary rash is macular or papular with various sized and shaped erythemato-squamous lesions the pintids or empeines Spirochetes are readily demonstrable in secondary lesions and serologic tests become positive in 60 percent or more of the cases According to some reports, secondary lesions never ulcerate but gradually, over a period of many months the early rash evolves into the tertiary lesions the dyschromic stage This late form is characterized by achromic or pigmented spots of various sizes localized mainly on the distal portion of the extremities but often over the trunk and face as well These lesions still contain spirochetes early in their development During the so called tertiary stage plantar and palmar hyperkeratosis has been reported at times with painful fissuring The cardiovascular and central nervous systems are said to be involved in an appreciable portion of cases although the findings in spinal fluid examination are reported to be normal Little has been written about bone involvement but severe bone pains have been reported in some cases During the late stage serologic tests are positive in 70 to 100 per cent of cases Gradually as the activity of the process diminishes only hyper or hypo-pigmented scarred areas remain[3, 34, 35, 36, 37, 38, 39] Descriptions of pinta give the impression that the lesions are superficial and produce little in the way of severe hypertrophic or destructive changes Leon Blanco and de Laosa state that the superficiality of the skin lesions is explained if there is taken into account the ectodermo tropism or more precisely the epidermo tropism of the treponema of pinta which contrasts with the mesodermo tropism of the treponema of syphilis [3]

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quired in childhood by direct or indirect contact or possibly through insect transmission a disease of primitive people whose hygienic habits are poor and among whom crowding affords ample opportunity for contact spread In many parts of North Africa childhood syphilis is so common that it is expected that every child will sooner or later be afflicted and Lacapere' stated that in Morocco there was clinical and serologic evidence of syphilis in more than 70 per cent of the Moslem population Apparently a primary lesion was seldom noticed but this is understandable in a group among whom ulcers and sores of many kinds are common A secondary eruption develops and circinate pemphigoid and ulcerative lesions are seen frequently Late destructive ulcerative lesions are observed often but neural involvement is said to be extremely rare[13] Ernst von During who was Professor of Syphilology at Constantinople Medical School from 1889 to 190 stated that in the Northwestern Provinces of Asia Minor syphilis was rarely venereal but was acquired usually in childhood Although severe and extensive destructive late lesions of the bones and skin were common in young adults there was not a single instance of tabes or general paralysis recognized among 80 000 cases Congenital syphilis was rare[14]

Variations in Adult Civilized' Syphilis

It is evident that while there are many similarities between these patterns of treponematosis there are also some differences However accurate quantitative data are not available to assess the significance and extent of these differences There can be no doubt that the childhood acquired primitive forms of treponematosis present a pattern which differs from adult civilized syphilis but adult syphilis itself does not produce a constant pattern and its manifestations vary somewhat in different racial groups

Frazier and Li Hung Chung analyzed the racial variations of the clinical patterns in adult urban syphilis as seen in Chinese in Peiping and in whites and negroes in Baltimore Each racial sample represented a series of consecutive patients admitted to the syphilis clinics of either the Peiping Union Medical College Hospital or the Johns Hopkins Hospital and although the samples were selected in that they represented patients seeking medical care at hospitals and thus may not be truly representative of the entire syphilitic populations of the areas from which they were drawn they probably provide comparable material on

In the treatment of pinta it has been found that the active skin lesions respond promptly to the preparations employed in syphilis, but that the residual leucodermic scars are unaffected, and frequently serologic tests remain positive[3, 4]

Irkintja

From Australia come reports of a treponematous disease which has been set apart by the aboriginal name irkintja, which is used by the natives of the area affected This disease has been described among the tribes of Central Australia for more than a century, and according to mythology it is thought to have existed there since ancient times Irkintja is a community disease which is contracted in childhood and probably results in a permanent immunity since second attacks are unusual It is characterized by an early period with a scattered skin eruption of flat papules most frequently grouped about the warm moist parts of the body Later severe ulcerative lesions, which may result in destruction of the structure of the central part of the face (gangosa) and extensive bone deformities develop Hackett has applied the term "boomerang leg" to describe the appearance of the deformity of the lower leg resulting from irkintja or yaws in Australia[40] Serologic tests usually are positive Little is known of neural or cardiovascular involvement in this condition Considerable confusion exists in the classification of irkintja some have called it syphilis while Hackett apparently believes it is yaws[40, 41] but from the description and photographs which Hackett has published[41] the florid framboesiform yaws papules appear to be lacking and the secondary eruption is relatively scanty and insignificant However typical yaws apparently occurs in Northern Australia which is tropical and has a high rainfall, while the irkintja area is semi-arid

Tribal or Primitive Syphilis

In addition to those clinical patterns of treponematosis called bejel, pinta irkintja and yaws there is in Africa Asia and the near East a vast reservoir of treponematosis which is designated as pandemic, tribal or primitive syphilis or by some similar title It is evident that tribal syphilis differs both epidemiologically and clinically from classical occidental syphilis[1] Epidemiologically it is a community disease, ac-

cured in childhood by direct or indirect contact or possibly through insect transmission, a disease of primitive people whose hygienic habits are poor and among whom crowding affords ample opportunity for contact spread. In many parts of North Africa childhood syphilis is so common that it is expected that every child will sooner or later be affected and Lacapère[1] stated that in Morocco there was clinical and serologic evidence of syphilis in more than 70 per cent of the Moslem population. Apparently a primary lesion was seldom noticed but this is understandable in a group among whom ulcers and sores of many kinds are common. A secondary eruption develops and circinate pemphigoid and ulcerative lesions are seen frequently. Late destructive ulcerative lesions are observed often but neural involvement is said to be extremely rare[11]. Ernst von During who was Professor of Syphilology at Constantinople Medical School from 1889 to 1900 stated that in the Northwestern Provinces of Asia Minor syphilis was rarely venereal but was acquired usually in childhood. Although severe and extensive destructive late lesions of the bones and skin were common in young adults there was not a single instance of tabes or general paralysis recognized among 80 000 cases. Congenital syphilis was rare[11].

Variations in Adult Civilized Syphilis

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the clinical findings in syphilitics as seen in the three racial groups in the two localities. It was brought out that syphilis is a disease not of youth but of sexual maturity, early lesions appearing on the average between 22 and 29 years of age, negroes having a somewhat younger age of infection than the other races. The onset in the third decade of life is quite at variance with the age at onset of tribal endemic syphilis, bejel, pinta and yaws, which are acquired usually in childhood.

Certain significant differences were observed in the evolution of the clinical patterns of syphilis in the three racial groups. The infection was latent in a smaller proportion of whites than in either of the other groups, while the Chinese had the highest ratio of latency. In cases classed as secondary syphilis involvement of the skin and mucous membranes was the commonest manifestation in all races but was most frequent in negroes and in females of all races. Among the cutaneous manifestations of secondary syphilis hypertrophic condylomatous lesions occurred in 20 per cent of male Chinese, 30 per cent of female Chinese, 12 per cent of white males, 26 per cent of white females, 17 per cent of negro males and 52 per cent of negro females. From this it would appear that Chinese and negroes react with more hypertrophic skin lesions than whites and that females of all races are more prone than males to the appearance of condylomatous lesions. Involvement of the skeletal structure during the secondary stage was most common among Chinese and least common among whites, the lesions occurring most often among males of whatever race. Localization of disease in bone and periosteum occurred in 21 per cent of Chinese males, 3.5 per cent of negro males and in 1.4 per cent of white males, while the corresponding figures for females was for Chinese 14.3 per cent, for negroes 2.4 per cent and for whites 0.9 per cent. During the secondary stage ocular lesions were present in a considerably higher proportion of negroes than in either of the other races.

In late syphilis the disease was predominantly one of extra-neural structures except in white males among whom manifest neural syphilis was almost twice as common as extra-neural and made up 64 per cent of all late manifestation. Neural syphilis occurred least often among negroes and most often in whites, being commonest among males in all races. Cardiovascular syphilis was more than twice as frequent among negroes as among the other two races and in general males were more often affected than females.

The authors suspect that in its incipiency the infection may tend to localize in one group of tissues to the exclusion of others and that

extensive and marked cutaneous reaction may protect neural structures In the Chinese group the severity of neural involvement varied inversely with the degree of cutaneous reaction Furthermore late in the disease concomitant cutaneous and neural involvement was extremely rare[4]

There appear to be then certain definite and well marked differences in the response of whites Chinese and negroes to syphilis the adult urban type of treponematosis The underlying causes of such differences are not clearly understood and probably depend upon a multitude of complex and as yet unmeasurable factors concerning the parasite the host and the environment Strains of *T pallidum* isolated from Chinese in China from such diverse anatomic sites as the cerebrospinal fluid a cutaneous gumma or the aorta have behaved in rabbits in respect to virulence and produced disease patterns in much the same way as strains of *T pallidum* isolated from negroes or whites in the United States Over a period of 15 years and involving more than 50 animal passages certain Chinese strains have shown no alteration in virulence or in the pattern of tissue localization[4] It is unlikely that differences in patterns of localization in certain tissues in humans can be explained wholly on the basis of tropism or virulence Whether race in itself is an influencing factor is debatable for races differ in their ways of life their dietary and hygienic habits and in countless other ways such as the type of clothing worn their physical and mental activity and the character of housing All those diverse factors may influence reaction to an infection, particularly one of such a long slow evolution as syphilis Physical environment dependent partly upon race and partly upon locality may have a profound effect upon a chronic disease through such influences as sunlight temperature humidity the fruitfulness of the soil and the abundance and type of vegetation

THE CAUSE GENUS TREPONEMA

In past centuries yaws was thought to arise from outside influences depending somewhat upon current superstitions Hermans[1] quoted Bontius writing of 164 which stated that the origin of the disease was in the special nature of the air and country the salt vapours from the sea or from certain types of food or drink Davies[14] writing about the same time attributed the disease to the bad nourishment of crabs while a contemporary Thomas Trapham[16] stated that the yaws was produced from the unnatural mixture of human with brutal seed

It was not until about the nineteenth century that it was generally believed that the disease was due to a contagion although as early as 1707 Hans Sloan[1] stated that "this distemper (yaws) is thought to be contagious and to be communicated from one to another"

With the development of the bacteriologic era the search for infectious agents as causes of disease became intensified In April 1905 Schaudinn and Hoffman[46] described spiral organisms found in the lesions of early syphilis but stated that further studies would be necessary to establish a causal relationship Seven months later an article by Castellani appeared in the British Medical Journal[1] describing similar organisms found in cases of parangi (yaws) Castellani stated that while examining films of secretions from ulcers from a case of parangi stained by Romanowsky's method he noted several "minute almost invisible spirochete like bodies" to which he did not attach much importance until later when Professor Schaudinn sent him a reprint of the preliminary note on finding spirochetes in syphilis Knowing the similarity between yaws and syphilis he began at once to investigate more cases of yaws and found similar or identical spirochetes in cases with early yaws lesions but like Schaudinn and Hoffman he was cautious in ascribing a causal relationship to the organisms and stated he did not desire to commit himself in any way as regards the etiology of parangi Confirmation of these findings soon came in abundance from many investigations in various parts of the yaws world and the tenuous spirochete *Treponema pertenue*, was accepted as the cause of the disease

Morphologically *T pertenue* and *T pallidum* are identical with tightly coiled spirals possessing the same characteristic motility Some observers have reported certain differences in structure or motility but none of these findings has stood the test of time Kitamura[48] made use of a device, by which he could observe preparations on two dark field microscopes at the same time so that half of each field could be studied simultaneously Careful comparison of a number of strains of each organism convinced him that the two were indistinguishable The dimensions of *T pertenue* vary from about 4 to 14 micra in length and from about 0 2 to 0 3 micra in thickness although longer forms are seen sometimes There are usually 6 to 12 regular spiral turns spaced about 1 micron apart Reproduction is presumed to occur by transverse division The time required for reproduction is not known with certainty but it probably does not differ much from that for *T pallidum* which is estimated to be about 30 hours[49, 50] The staining qualities are also similar[51] and although the treponemata are generally more difficult

to stain than bacteria they take up various organic dyes The most satisfactory preparations are made however with some of the silver impregnation methods Cultivation of *T pertenue* has been attempted and although success was claimed by Noguchi it is generally held that cultivation has not yet been accomplished with either *T pertenue* or *T pallidum*

As far as is known *T pertenue* does not long survive outside the mammalian host of which man is the only natural reservoir although other animals including rabbits apes and monkeys may be infected experimentally The organism quickly loses motility outside the body being especially susceptible to drying Yasuyama[53] has shown that *T pertenue* from infected monkeys when kept at 37 C in saline or serum retains infectiousness for at least one to two hours that motility is considerably decreased within 3½ hours and disappears within 4 hours In a study of the possible role of insects in yaws transmission it was found that *T pertenue* remained actively motile in the esophageal diverticulum of a small fly *Hippelates pallipes* for about 7 hours after feeding on yaws lesions rich in spirochetes[4] Both *T pertenue* and *T pallidum* may be preserved in a virulent state for long periods of time when kept at very low temperatures approximately −78 C but both organisms are killed when subjected to a process of freezing and desiccation [4]

Spirochetes are found in large numbers in nearly all types of skin lesions of the early stage of yaws In the primary stage they may be demonstrated as soon as a noticeable lesion appears although it may be necessary to abrade the surface to obtain serum Later when the typical crusted superficially ulcerated papule develops there is usually a profuse weeping of straw colored serum from the surface after removal of the crust with myriads of actively motile treponemes present in the serum Enlarged lymph nodes either satellite buboes of the primary lesion or occurring during the generalized secondary stage may be shown by lymph node puncture to contain spirochetes Organisms are also circulating in the blood during early stages and Castellani[7] was able to transmit yaws to a monkey using blood of a patient with early yaws lesions Although spirochetes have been demonstrated on rare occasions in juxta articular nodules[3] and in gummatous ulcerations as a rule they cannot be found in late lesions

The etiologic agent of yaws then is a tenuous spiral organism an obligate parasite which is normally specific for man which is fragile

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ported and it is not to be doubted that the disease was introduced repeatedly from West Africa and the West Indies Fox refers to numerous accounts of its occurrence in the United States during the 18th century mainly in the South but between that time and 19 2 the date of his report of an additional case he was able to find records of only 10 United States cases in the medical literature[61] Since then a few sporadic case reports have appeared nearly all of them either representing infections imported from endemic areas or being open to serious doubt as to the accuracy of diagnosis which usually was based upon the exuberant hypertrophic character of generalized lesions and upon the rapid response to therapy neither of which criterion is a valid differential point Such a case is that reported by Cady and Engman[6] which occurred in Missouri in 19 3 The patient a 7 year old negro who had never been outside the United States first developed small nodular wart like lesions in front of his left ear and during the following 3 months widespread hard smooth slightly elevated papules appeared including a lesion on the hard palate Physical examination revealed scattered grouped follicular lesions circinate lesions and plaques some being granulomatous Serologic tests were positive and treponemes were found in material from the lesions The patient was treated with five injections of neo-arsphenamine over a period of about weeks during which the lesions healed rapidly and the Wassermann reaction was negative 10 days and 2 months later Neither the clinical pattern nor the rapid response to a minimum amount of treatment is proof of the diagnosis of yaws for the same situation is encountered in syphilis not infrequently A more authentic case is that reported in 1948 by Post and Sheard[62] in a 14 year old negro boy who had returned recently to New York City from Martinique and who showed a primary lesion on one lower leg a frambоesiform secondary eruption and hyperkeratotic palmar and plantar lesions Serologic tests were positive and treponemes were demonstrated in secretions from skin lesions

We may be fairly certain that although yaws cases were introduced in the United States in large numbers two or three hundred years ago and sporadically since that time yaws as such has failed to persist as an endemic disease Possibly this may be due to the fact that some unknown environmental factors favorable to the transmission of the disease are lacking or because the character of the disease is modified by the environment in such a way that transmission is impeded or finally it may be that transmission of spirochetes from yaws cases is occurring

and quickly dies outside the body and which is found in large numbers in the early lesions of yaws

EPIDEMIOLOGY

World Distribution

Yaws is generally limited strictly to those tropical areas of the world where enviromental conditions favor its development and spread Where the disease is prevalent, there is nearly always found a moderate to heavy rainfall a warm climate an abundant vegetation usually of the jungle type and a primitive population of low hygienic level, whose clothing is scanty, and who crowd together to sleep Given these conditions, yaws is found nearly everywhere and in some regions the level of infection reaches the saturation point For example 60 per cent of a population group in Jamaica B W I had yaws and more than 75 per cent of the children had been infected before they reached 15 years of age[9] The distribution of the disease is often spotty and heavily infected areas may be found adjacent to areas where there is little or no yaws This was found to be especially striking in Jamaica where rural population groups nearly saturated with yaws were found within a few miles of other groups among whom the disease was practically absent[9]

The world prevalence and distribution of yaws is constantly changing The effects of improved hygiene energetic yaws control measures urbanization of population groups and destruction of forests have brought about a decline in prevalence and the disease has disappeared from some countries where it once was prevalent On the other hand yaws doubtless has increased in some areas as a result of disruption of control measures increased poverty decline of hygienic levels and migration of yaws infected peoples brought about largely by the recent world war Therefore the world geography of yaws will vary from time to time and the figures for one time and place may be true only at that instant The following account of the world distribution of yaws is based mainly upon personal observations official government reports published articles and personal communications gathered over a period of years The material collected before 1936 was summarized in the Report of the Jamaica Yaws Commission for that year[60]

North America — Yaws apparently was not uncommon in the Southern United States during the period when slaves were being im-

sporadic cases occur in the mining area of the Union of South Africa. The disease is practically unknown in Eritrea and in British, French and Italian Somaliland and it is not reported except in rare instances from Morocco, Algeria, Tripoli or Egypt. However, tribal syphilis is extremely prevalent in certain parts of North Africa and other areas where yaws is rare.

Asia.—Yaws is common in some parts of India and although formerly very prevalent in Ceylon, during the past several years the disease is seen much less frequently as a result of an organized treatment campaign. It is common throughout parts of Burma, most of French Indo-China, Thailand and the Malay Peninsula. Sporadic cases are reported from parts of southern China and from Formosa.

The East Indies and the Pacific Islands.—Yaws is very common in large areas of the Netherlands Indies, the Philippines, New Guinea, Sarawak, Brunei and British North Borneo. It is prevalent and one of the main causes of morbidity throughout most of the islands of the South and Southwest Pacific area. In the Hawaiian Islands, however, the disease is unknown. It is common in the tropical parts of northern Australia, and a pattern of primitive syphilis, said by some to be yaws, sometimes called irkintja, is prevalent in the arid central part of that country.

Yaws, a vast tropical reservoir of treponematosis, is a world problem of great magnitude and importance. It is one of the most frequent causes of disability among population groups throughout much of the tropical world. The size of the problem can only be estimated because exact figures of prevalence are not available. A decade ago in the West Indies the number of cases reported as treated during one year amounted to 275 000 or nearly 3 per cent of the total population of the areas reporting. Between 1932 and 1936 the Jamaica Yaws Commission alone treated nearly 5 000 persons for yaws[60] and before the last war there were probably two million cases treated each year throughout the tropical world and doubtless for many more millions treatment was not available.

Environmental Factors Related to Yaws Prevalence

Through all the literature on yaws runs the ever recurring refrain of warm moist climate, dense vegetation, primitive peoples wearing scanty clothing and crowding together in their shelters, childhood infection, an exuberant granulomatous skin eruption early in the disease and

but that the resulting disease pattern is indistinguishable from American syphilis

Mexico, Central America and the West Indies — Yaws is not reported from Mexico British Honduras Nicaragua or El Salvador, although environmental conditions favorable to the spread of yaws exist in some parts of the low coastal plains and there is a constant interchange of population with nearby yaws endemic areas One wonders if the disease does not occur but is either not being recognized or reported or perhaps is being confused with some other condition such as pinta which is common in parts of Mexico Endemic yaws is said to exist in certain parts of Guatemala Honduras Costa Rica and Panama It is prevalent in most of the West Indies especially in Jamaica Haiti and the Dominican Republic and it is also said to be common in Nevis St Kitts, Anguilla, Antigua Montserrat Guadalupe Dominica, Martinique, St Lucia St Vincent Grenada Trinidad and Tobago It is absent from the Bahamas and although once prevalent in Barbadoes, it is reported to have disappeared from that island A few cases have been described in the past from isolated foci in Cuba and Puerto Rico but at present the disease is not found Yaws was common in the Virgin Islands during the period of the slave traffic but has disappeared since and an intensive survey of the population of the Islands of St Thomas and St Croix showed that syphilis was common about 18 per cent of the Negro population giving positive serologic tests but not a single case resembling yaws was seen during the examination of more than 1 000 people[61]

In *South America* yaws probably is common throughout much of Colombia Venezuela and British Dutch and French Guiana It is prevalent in the forested parts of Brazil in the Northern and Eastern regions of Ecuador and in Peru along the Eastern slopes of the Andes and in the jungle lowlands It is not reported from Bolivia, Paraguay, Uruguay, Argentina or Chile

Africa — Yaws is widespread and very prevalent throughout most of the forested areas of tropical Africa where there is abundant rainfall including French West Africa Gambia Sierra Leone Liberia the Gold Coast Southern and Southeastern Nigeria Cameroon Southern French Equatorial Africa and the Belgian Congo It is prevalent in parts of Uganda Kenya Tanganyika and there are a few foci in Nyasaland Much of Madagascar is heavily infected During the second World War yaws was one of the major causes of disability among West African troops large numbers of whom had bone and joint lesions[6] A few cases are reported occasionally from Northern and Southern Rhodesia and

sporadic cases occur in the mining area of the Union of South Africa The disease is practically unknown in Eritrea and in British French and Italian Somaliland and it is not reported except in rare instances from Morocco Algeria Tripoli or Egypt However tribal syphilis is extremely prevalent in certain parts of North Africa and other areas where yaws is rare

Asia — Yaws is common in some parts of India and although formerly very prevalent in Ceylon during the past several years the disease is seen much less frequently as a result of an organized treatment campaign It is common throughout parts of Burma most of French Indo-China Thailand and the Malay Peninsula Sporadic cases are reported from parts of southern China and from Formosa

The East Indies and the Pacific Islands — Yaws is very common in large areas of the Netherlands Indies the Philippines New Guinea Sarawak Brunei and British North Borneo It is prevalent and one of the main causes of morbidity throughout most of the islands of the South and Southwest Pacific area In the Hawaiian Islands however the disease is unknown It is common in the tropical parts of northern Australia and a pattern of primitive syphilis said by some to be yaws sometimes called irkintja is prevalent in the arid central part of that country

Yaws a vast tropical reservoir of treponematosis is a world problem of great magnitude and importance It is one of the most frequent causes of disability among population groups throughout much of the tropical world The size of the problem can only be estimated because exact figures of prevalence are not available A decade ago in the West Indies the number of cases reported as treated during one year amounted to -75 000 or nearly 3 per cent of the total population of the areas reporting Between 193- and 1936 the Jamaica Yaws Commission alone treated nearly 5 000 persons for yaws[4] and before the last war there were probably two million cases treated each year throughout the tropical world and doubtless for many more millions treatment was not available

Environmental Factors Related to Yaws Prevalence

Through all the literature on yaws runs the ever recurring refrain of warm moist climate dense vegetation primitive peoples wearing scanty clothing and crowding together in their shelters childhood infection an exuberant granulomatous skin eruption early in the disease and

frequent deforming bony involvement and destructive skin lesions later on There are many variables which might affect yaws prevalence including climate location vegetation insect vectors age, sex and race of the population concerned their living habits, type of housing and social economic and hygienic level

Climate and Yaws — Climate is a composite of many factors, temperature, humidity precipitation as rain or snow, wind sunshine and others The influence of some of them on yaws prevalence has been emphasized frequently and more or less accurately measured by epidemiologic studies

Temperature itself appears to be an important limiting factor, for yaws is never found in areas with cold freezing temperatures Hermans stated that he was convinced of the influence of climate on the occurrence of yaws and that in the cold season of the year the disease affects chiefly the axillae the nates and palms of the hands and the soles of the feet whereas in the warm part of the year we see the typical spread over the whole body When it is warm and damp the typical papules appear When it is cold and dry, the skin is much less apt to react with overgrowths'

Studies in Jamaica[9] revealed that while yaws had been repeatedly introduced into all parts of the island it had remained localized in sharply delimited areas for many decades or centuries Although there was considerable temperature variation with altitude and with season this factor probably was of little importance in influencing prevalence of the disease because the climate was warm everywhere The amount of rainfall appeared to be important and everywhere that yaws was prevalent (from 40 to 90 per cent of the population infected) the annual precipitation amounted to 50 inches or more The disease was never highly prevalent in any area where the average annual rainfall was less than 40 inches On the other hand in a number of areas where yaws was found to be absent the average rainfall was as high as 52 to 98 inches a year but all of these locations were at a higher elevation (about 1,500 feet) than areas with more yaws and with equal or greater precipitation At these higher elevations the lower temperatures which prevail may have had a suppressing effect on the evolution of early infectious lesions

In India numerous observations were made on the effect of climate upon the disease Mukharji[66] stated that yaws was prevalent mostly *during* the rainy season some cases running a latent course in the dry winter season only to have lesions reappear during the following wet season Iyer[4] said that although the disease was seen throughout the

year the rainy months (July to October) appeared to be more favorable for transmission In Burma the report of the Public Health Administration for the year 19 8 stated that plantar lesions of yaws become exacerbated during the rainy season when painful cracks and fissures develop In Brasil too the relationship between climate and yaws was noted by Ferreira Lopez[68] who wrote I have observed the decisive influence of rainfall on yaws principally on certain types of lesions and after the rains the granulomata are predominating In the dry season we found more of the hyperkeratotic type

Lopez Rizal and Sellards[6] gave an interesting account of the clinical differences between yaws cases seen in the Philippines in the warm humid lowlands and those seen in a mountainous area of Northern Luzon at an altitude of 2 500 to 3 700 feet The authors recorded the temperature differences between the two locations but unfortunately did not comment upon rainfall The average monthly minimum temperatures for the mountainous locality ranged from about 58 F to 61 F and for the lowland area from about 70 F to 77 F while the average monthly maximum temperatures for the mountain area ranged from about 80 F to 90 F and for the lowland area from about 87 F to 95 F

Only about one half of the cases seen in the mountains were in children the remainder a surprisingly high proportion being in adults The patients showed involvement chiefly of the mucocutaneous tissues about the mouth nose anus and genitalia Of 33 cases lesions about the anus or genitalia were seen in 29 and about the mouth or nose in . Usually the disease ran its entire course without the development of generalized granulomata over the body and only 5 of the 33 cases showed evidence of metastatic involvement of the skin in areas more or less remote from the mucocutaneous lesions In a larger group of . cases seen in the mountain province only 19 showed metastatic lesions The authors stated that morphologically the lesions looked like syphilitic condylomata and furthermore that there was some indication of transmission by sexual contact In contrast the cases seen in the lowlands showed characteristically the typically florid generalized framboesiform eruption

Of particular interest and bearing on the question of the effect of climatic environment upon yaws is the description by Scott[70] of an epidemic of yaws among the negro employees of the Witwatersrand mines in South Africa Yaws does not occur in South Africa except for sporadic cases imported from known endemic areas The Witwatersrand which is situated on a high rather barren plateau about

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6 000 feet above sea level has an annual rainfall of only about 30 inches Temperatures are far from tropical with many degrees of frost during the winter Thus the climate is completely different from that where yaws is found normally

Between 1915 and 1925 occasional cases of yaws had been diagnosed by the mine medical officer among the workers of one of the mines the Turf Between 1925 and 1931 coincident with a change of medical officers, similar cases were diagnosed and treated as syphilis However in 1931 Scott found that yaws was prevalent among certain groups of workers, among whom 338 cases were found during that year 116 cases appearing during the first six months of the year and 2 during the last six months There were about 8 000 natives working at the mine site in 1931 some having been recruited from Portuguese East Africa, where yaws was prevalent and some from British South Africa where only sporadic cases existed However the new cases of yaws in 1931 appeared as frequently among British South Africans as among the others indicating that the disease was being acquired at the mine Of the 8 000 boys' as the native workers are called 000 were housed in one compound the Turf and all worked down the Turf shaft The remaining 6 000 boys were quartered in another compound the Main' 4 000 of them worked down the Chris shaft and 1 000 down the Turf shaft 1 000 others remained on the surface during the entire time Sanitary bathing and housing facilities in the compounds were adequate There was monthly medical inspection of laborers during which the majority of yaws cases should have been detected readily

The striking feature of the distribution of cases among the various groups was that of the first 54 cases developing during 1931 246 (about 98 per cent) were in boys working down the Turf shaft only 8 cases being found among those working in the Chris shaft, and not a single case was seen among the boys working on the surface Furthermore the distribution of cases between the two compounds was about in proportion to the numbers working down the Turf shaft 162 boys with yaws lived in the Turf compound (2 000 laborers to Turf shaft) and 92 lived in the Main compound (1 000 laborers to the Turf shaft) Eighty four per thousand Turf shaft natives were affected 2 per thousand Chris shaft boys and none of the surface boys This was not just a temporary condition which occurred during 1931 because records showed that sporadic cases had been appearing among Turf shaft workers for many years Scott reported in 1935[11] that during the first 9 months of that year there had been 69 cases of yaws 64 from the Turf

shaft and 5 from the Chris shaft, the cases being divided about equally between East Coast and British South African natives.

That the disease was in fact a treponematosis was demonstrated both by positive serological tests and by the presence of spirochetes on dark field examination, and Scott's clinical description and photographs leave no doubt that the cases were typical florid yaws. Primary lesions were not seen on the feet or ankles, which is probably explained by the fact that at work the boys wore boots extending well up the calf. The facts presented by Scott point to the conclusion that transmission not only took place underground but almost entirely in the one shaft. No explanation of this remarkable distribution of cases was offered, and no description was given of differences which might have existed between environmental factors in the two shafts. However, yaws did not develop in employees working on the surface where the climate was dry and cool in summer with subzero temperatures in winter. In the mines, however, extending 6,000 or more feet below the surface, "the workers are bathed in perspiration, the temperature at their working place varying from 87° F. wet bulb and 88° F. dry to 91° F. wet bulb and 9[illegible]° F. dry."[10] Here then is an example where climatic environment undoubtedly has been a major factor in determining the propagation and development of yaws. The disease appeared only in underground workers who spent a large part of their time in a hot, humid environment, while boys who spent all their time in the cool, dry climate of the surface were unaffected.

Rainfall and Yaws in Jamaica.—Evidence in support of the belief that rainfall somehow affects the evolution of the secondary eruption of yaws is available from Jamaica.[9] Treatment teams of the Jamaica Yaws Commission surveyed numerous adjacent areas in highly infected territory during or after the dry season; others were studied during or after the rainy season. In each area all persons found during preliminary surveys by trained lay personnel to have latent or manifest yaws of less than 5 years duration, or to have some clinical type of late yaws regardless of duration of infection, were examined in clinics by physicians. Striking differences were noted in the number and type of yaws lesions found during wet and dry seasons. In the rainy months a greater proportion of patients were found with open, infectious types of lesions, and generalized framboesiform papules were more numerous, larger, and more succulent. During dry seasons hypertrophic papules were fewer in number and were localized more often about the warm, moist parts of the body, and the secondary eruption was more often of a dry, scaling

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maculo papular type Treatment given to patients with clinically manifest yaws was followed by disappearance of lesions in most cases Subsequently in many areas re-examinations of yaws patients were made at intervals of several months It was found that the infectious relapse rate was roughly proportional to the amount of rain which fell between the initial and follow-up periods Expressed statistically there was found to be a high degree of correlation between the average monthly rainfall for a period of three months preceding the examination of a population group and the percentage of early yaws cases showing typical framboesiform papules For example, in five areas with an average monthly rainfall of less than 10 inches ranging from 2 05 inches to 9 17 inches, the proportion of early yaws cases with framboesiform papules ranged from about 8 to 29 per cent while in another five areas with an average monthly precipitation of more than 10 inches *ranging from 10 9 inches* to 40 5 inches the proportion of early yaws cases with framboesiform papules ranged from 31 per cent to nearly 38 per cent In nine areas where control measures were carried out a careful record was kept of new yaws infections developing during a three-year period Again there was found to be a high correlation between rainfall and the incidence of new infections

Hackett discussed the relative frequency of yaws and syphilis in two districts in Uganda At Lira located about 3,600 feet above sea level the average number of new yaws cases recorded each year was 3 077 while the average number of new cases of syphilis was 164 At Masaka about 200 miles southwest of Lira at an altitude of 4,300 feet the average number of new yaws cases recorded each year was 266, the new cases of syphilis, 2 818 Lira the yaws area is at a lower altitude is somewhat warmer and has a higher rainfall than Masaka At Lira the annual maximum and minimum temperature values were 86 7°F and 62 3°F and at Masaka, 79 6°F and 61 1°F The annual rainfall at Lira was 56 56 inches while that for Masaka was 49 41 No mention was made of other environmental differences which might influence disease prevalence such as the type and density of vegetation the habits of the population and their hygienic level Descriptions were given of the type of lesions found in 190 cases diagnosed as secondary syphilis Scrotal anal and perineal condylomata were noted in 91 patients, but mention was not made of framboesiform lesions Penile sores were present in 60 cases It was stated that there was a higher proportion of children in the yaws group at Lira than among the syphilis group at Masaka There is an interesting similarity in the situation in Uganda

with that described by Lopez Rizal and Sellards[9] in the Philippines It is possible that in these two areas a gradual transition in the disease pattern is taking place the secondary eruption becoming limited more to perianal genital and perioral regions in the higher colder drier areas This change in pattern would tend to make the disease less readily transmissible by the casual bodily contacts of childhood and require more intimate contact possibly sexual and therefore more apt to happen in adults If such a change in yaws takes place, with the practical disappearance of the framboesiform papule the type of lesion which gives yaws its name then the strict localization of framboesia to warm moist areas of the world is more easily understood In the absence of a profuse framboesiform rash the disease is called by some other name

Evidence strongly suggests that climatic factors of warmth and moisture favor the propagation and development of yaws Framboesia does not prevail where either of these factors is absent but there are inhabited areas of the world possessing favorable climatic conditions in which yaws does not become endemic although repeatedly introduced The reasons for this are not clear

Altitude in Relation to Yaws — It is probable that altitude of itself has little if any effect on yaws but indirectly it may be important by influencing temperature rainfall vegetation and fashions in clothing Although yaws has been found over a wide range of altitude from sea level to more than 6 000 feet it is prevalent only under conditions of sufficient warmth moisture and most likely abundant vegetation In Jamaica[9] the disease was most prevalent in inland mountainous districts but it was common also in low lying valleys and no correlation appeared to exist between elevation and prevalence In Java the experience has been that yaws is a disease occurring chiefly in the warm lowlands that its incidence decreases gradually in proportion to the altitude and that it is absent from the plateaus On the other hand in Sumatra many cases are found at an elevation of 3 000 feet which is higher than the plateaus of Java[1,69] Factors other than altitude must be operating to produce such differences

Possible Influence of Vegetation — It is generally accepted that yaws is a disease of the jungles and forests and that it is seldom found in arid territory or in grasslands From Brasil Ferreira Lopez[73] reported that in the state of Minas Geraes yaws was found only in the forest zone with a hot humid climate and that in the open part of the country where the vegetation was low and the climate was dry the disease was not seen Vargas[74] wrote about Colombia there is pian (yaws) in the Magdalena

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there are forms of treponematosis labelled by such names as tribal syphilis or bejel The similarity of these patterns to yaws has been noted There is childhood transmission a high community incidence and condylomatous lesions are frequent Neural and cardiovascular involvement apparently is rare In fact if the typical hypertrophic, framboesiform type of lesion were a frequent and characteristic feature of the patterns in North Africans and Arabs the disease probably would be labelled yaws It is to be remembered that the yaws eruption apparently is modified by climate so that exuberant granulations of the secondary rash are suppressed by cold dry conditions It is interesting to speculate on what would result if it were possible to transfer a group of florid yaws cases to North Africa or Arabia and a number of cases of childhood tribal syphilis or bejel to the jungle regions of West Africa It is probable that the transplanted yaws cases would tend to look less and less like yaws the generalized lesions becoming less prominent and more localized to the warm moist parts of the body and that the cases of bejel or tribal syphilis would tend to produce a more exuberant eruption

Hygienic, Social and Economic Factors — Yaws is a crowd disease It flourishes in surroundings where there is poverty uncleanliness and poor housing warmth moisture and shade The majority of the yaws-infected populations of the world are from our point of view primitive poor unclean and crowded But even in yaws areas there are gradations in respect to living standards and different social strata may be well defined In one study of two rural communities in Jamaica[56] the prevalence of yaws among children of the upper class was compared with the prevalence among children of the lower class Taking the family as a unit the residents of each area were divided into the two classes according to their social and economic standing as judged by such evidence as size and appearance of the home the cleanliness of the home and premises personal cleanliness and manner of dress Families of the upper class comprised the better educated people in each of the areas and included teachers minor government officials tradesmen and small landowners In the lower class were families of the large peasant or laboring group most of whom were careless and uncleanly in their dress and personal habits Although the children of both classes mingled freely and attended the same schools it was found that children of the upper class had significantly less yaws than the poorer children In two other yaws areas in rural Jamaica[77] a study was made of a random sample of 180 homes of families with children less than 15 years of age Each house was graded into one of three classes good fair or poor on the basis of

Valley, but only in those regions covered by thick woods and Dr Moreno Perez our epidemiologist, claims that it will disappear with the clearing of the forests

In Jamaica too yaws was found only in areas with an abundant vegetation but the reason for this relationship was not clearly understood An abundant vegetation of the jungle type requires as a rule an ample rainfall (or available ground water), environmental temperatures, which are not too low and a fertile soil The character of vegetation and soil depend to a certain extent upon underlying geological formations Some of them may be porous and dry Others may weather to a poor soil or they may provide relatively impervious, fertile soil which will support abundant vegetation Chambers stated that yaws was not prevalent in all areas in Jamaica where rainfall was abundant He believed that other factors favoring moisture such as the quality of the soil the shade of surrounding mountains and the density of vegetation also predispose to a heavy yaws incidence A dense cover of forest by itself may have an effect on yaws Forests hold moisture, they provide shade which prevents drying of soil and undergrowth The presence of dense vegetation usually offers more opportunities than a cleared area for cuts and scratches particularly on the legs and feet which may serve as portals of entry for *T pertenue* Furthermore, shade and moisture favor the survival of spirochetes in secretions from yaws lesions whether on the skin of yaws sufferers or on the surface of inanimate objects

In the Virgin Islands syphilis is common[61] but yaws is absent although it has been introduced repeatedly in the past The population group is largely negro and predominantly rural and social economic and hygienic standards and living habits[6] do not differ materially from those of many groups in Jamaica and elsewhere among whom yaws prevails However certain environmental factors are much different in the Virgin Islands than in yaws areas Although the climate is as warm with a range of temperature from 68 F to 92 F the rainfall is less abundant (annual precipitation of about 46 inches) is mostly seasonal and there are many months of the year when the climate is semi arid Furthermore vegetation is scanty much of the territory is open grass land or cane fields or there are scattered scrubby trees This is the type of terrain climate and vegetation which was associated in Jamaica with low yaws incidence

In the semi arid and desert regions of North Africa and in the Euphrates area where rainfall is scanty where freezing winter temperatures are encountered and where there are no heavily wooded areas

nemes regardless of color of skin or ancestry With equal exposure yaws probably will result with equal frequency in all races It has been suggested from time to time that whites because of racial characteristics possess resistance to infection which is lacking in negroes It is true that yaws seldom is found in whites but this undoubtedly results from less opportunity for exposure Whites usually have better hygienic habits and environment than the black or brown primitive races and in addition white persons tend to avoid physical contact with obvious yaws cases In short customs habits and hygienic environment and not host factors are largely responsible for racial differences in incidence

Yaws has been reported to be prevalent among many differing indigenous racial groups including negroes in Africa and in the West Indies and in East Indians Indo-Chinese Filipinos Polynesians and Melanesians Whites may be infected where opportunity for exposure exists Scott reported [9] that seven white miners contracted yaws in the Turf mine in South Africa during the outbreak of yaws at that location and numerous other apparently authentic cases of yaws in whites have been described Magnuson has stated that there is no evidence of true racial immunity to syphilis in man although the course of the disease and its clinical manifestations may show racial variation [8] Doubtless this is true also of yaws However community susceptibility as expressed by the incidence of yaws in the herd may be influenced by differences in racial reaction to treponemal infection It is well known for example that early syphilis in Chinese and in negroes is characterized frequently by a papular rash and by condylomata while in whites these highly infectious lesions occur less frequently [4, 19] As a consequence of the greater prevalence of the more infectious types of lesion in one race it is to be expected that disease incidence would be greater than in other races with fewer such lesions By analogy it is probable that these racial differences occur in yaws as well as in syphilis but data are not available on this point

The Age and Sex Incidence of Yaws

It has been emphasized repeatedly that yaws is predominantly a childhood disease usually contracted before 15 years of age and that the majority of cases with active lesions are in children However non immunes may acquire the infection later in life and relapsing lesions may occur many years after the primary lesion has healed Childhood spread

light, air cleanliness bathing facilities and crowding (as measured by the available square feet of living space for each inmate) There was found to be a much greater yaws prevalence in the poorer, more crowded homes But when a comparison was made between homes in parts of Jamaica where yaws was found seldom or not at all, and homes in areas where the disease was prevalent it was found that the general sanitary level was much the same in all areas [9] It may be concluded that, although the sanitary level is an important factor in determining yaws prevalence, it is not the only one

Urban and Rural Prevalence – Yaws is predominantly a disease of rural areas and is seldom prevalent in cities and towns It is a common experience to find only rare cases in villages even small ones, although the disease may be exceedingly common in surrounding territory This was particularly true in Jamaica where careful surveys for yaws permitted an accurate measurement of prevalence [9 59] One district included a large town which was a commercial and fruit trading center with a railroad station a post office and a few tarred streets Among children 10 to 14 years of age a diagnosis of yaws was made in about 26 per cent of the town children and in about 52 per cent of country children Comparable situations were found in other areas There is no ready explanation for such great differences in yaws prevalance as between rural populations and those living in villages and towns The general sanitary level may have been slightly lower among rural families, but the difference was not great It is possible that treatment for yaws was more available and more utilized by people living in towns but it is not felt that this factor was of much importance Undoubtedly other factors in the district itself determined the differences in prevalence When compared with the surrounding countryside, villages and towns generally had less vegetation the lack of which might lessen the chances of injuries to the lower legs and feet, where primary yaws lesions usually appear Furthermore, abundant vegetation by providing shade and favoring the retention of moisture might have an important influence on the course of the disease itself Another factor which will be discussed in connection with the manner of transmission of yaws, is the influence of vegetation upon potential insect vectors especially small flies, *Hippelates pallipes*, which are found in abundance only where moisture and shade are available

Racial Factors —No true racial variation in susceptibility to yaws spirochetes is believed to exist and probably no significant immunity is present in persons who have not had a previous infection with trepo

nemes regardless of color of skin or ancestry. With equal exposure yaws probably will result with equal frequency in all races. It has been suggested from time to time that whites because of racial characteristics possess resistance to infection which is lacking in negroes. It is true that yaws seldom is found in whites but this undoubtedly results from less opportunity for exposure. Whites usually have better hygienic habits and environment than the black or brown primitive races and in addition white persons tend to avoid physical contact with obvious yaws cases. In short customs habits and hygienic environment and not host factors are largely responsible for racial differences in incidence.

Yaws has been reported to be prevalent among many differing indigenous racial groups including negroes in Africa and in the West Indies and in East Indians Indo-Chinese Filipinos Polynesians and Melanesians. Whites may be infected where opportunity for exposure exists. Scott reported[9] that seven white miners contracted yaws in the Turf mine in South Africa during the outbreak of yaws at that location and numerous other apparently authentic cases of yaws in whites have been described. Magnuson has stated that there is no evidence of true racial immunity to syphilis in man although the course of the disease and its clinical manifestations may show racial variation.[8] Doubtless this is true also of yaws. However community susceptibility as expressed by the incidence of yaws in the herd may be influenced by differences in racial reaction to treponemal infection. It is well known for example that early syphilis in Chinese and in negroes is characterized frequently by a papular rash and by condylomata while in whites these highly infectious lesions occur less frequently.[4, 79] As a consequence of the greater prevalence of the more infectious types of lesion in one race it is to be expected that disease incidence would be greater than in other races with fewer such lesions. By analogy it is probable that these racial differences occur in yaws as well as in syphilis but data are not available on this point.

The Age and Sex Incidence of Yaws

It has been emphasized repeatedly that yaws is predominantly a childhood disease usually contracted before 15 years of age and that the majority of cases with active lesions are in children. However non immunes may acquire the infection later in life and relapsing lesions may occur many years after the primary lesion has healed. Childhood spread

of yaws is a feature of the disease everywhere, and in this respect it is epidemiologically similar to "tribal syphilis" bejel and pinta

The prevalence of the disease by age and sex may be determined fairly accurately from a clinical history of infection with or without such corroborative evidence as active lesions positive serologic tests or characteristic scars One may question the accuracy of diagnoses based upon such historical evidence alone especially among native peoples but in one area in Jamaica where language difficulty was not a problem additional supporting evidence laboratory and clinical, confirmed the diagnoses in 97 per cent of persons giving a history of yaws of 10 years' duration or less[59] A study of the age distribution of yaws including latent cases in a group of 1 000 persons in rural Jamaica[80] showed that prevalence increased rapidly in childhood reaching a peak at about 10 to 15 years of age in males and about 10 years later in females after which there was a gradual decline in succeeding age groups (Table I)

TABLE I*

AGE AND SEX DISTRIBUTION OF YAWS IN JAMAICA

Age in Years	Percentage with Yaws Males	Females
0-4	18 8	18.4
5-9	55 8	47.0
10 14	78.0	64 7
15 19	[illegible]6	[illegible]5 8
[illegible]0-[illegible]4	[illegible]	[illegible]1.0
25 [illegible]9	74 8	[illegible].0
40 45	[illegible]6 2	61 2
50 55	[illegible]3 7	59.4
60-[illegible]5	[illegible]3 8	54 6
75 [illegible]9	55.4	54 3

This table for selected age groups was condensed from material given in reference No 80

From Table I it can be seen that during the first five years of life there was essentially the same proportion of males and of females with yaws but that after this period prevalence increased more rapidly in males so that a higher peak (78 per cent) was reached at an earlier age than in females in whom the greatest prevalence (71 per cent) was attained 10 years later at [illegible]0 to [illegible]4 years of age After infancy yaws was more prevalent in males in all age groups and was found in about 57 per cent of 10 616 males and in about 50 per cent of 11 050 females of all ages

The divergence in prevalence in the two sexes may be explained on the basis of differences in their activity and habits It is thought that yaws usually is acquired from the implantation of treponemes upon a pre existing wound commonly on the lower legs and feet Males both in childhood and as adults because of their greater physical activity, are more liable to such injuries During infancy these differences are not so marked and yaws occurs about equally in the sexes

The level of yaws infection, which is reached in any particular age group is dependent upon the rate at which new infections appeared in previous years of life experience This may be expressed as attack rates among persons of either sex with no previous yaws infection and therefore presumably non immune Such rates have been computed for the population group in Jamaica among whom yaws prevalence levels have already been described[80] Infection rates for males and females from birth to age 25 to 29 years are shown in Table II Rates for males are

TABLE II*

ANNUAL YAWS INFECTION RATES PER 100 NON IMMUNES (JAMAICA)

Age Group in Years	*Annual Infection Rates*	
	Males	*Females*
0-	1 4	1 4
1	9 9	7.0
2	12.6	10.9
3	11 3	12.8
4	19.6	14 5
5	18 6	13 8
6	2 .6	18.6
7	27.0	19 1
8	7 2	21.9
9-	33	19.0
10-14	20.9	12.8
15 19	9	5 2
20 24	3.0	2 3
25 9	1 6	1 1

* This table was condensed from material given in reference No 80

seen to increase rapidly from birth to 9 years of age and then to drop off sharply This would indicate that effective exposure which is low in infancy increases rapidly during early childhood to reach a high level at 8 to 10 years of age and then decreases again to a relatively low level The rates for females generally parallel those for males but at an appreciably lower level The maximum rate for females although never

of yaws is a feature of the disease everywhere, and in this respect it is epidemiologically similar to tribal syphilis bejel and pinta

The prevalence of the disease by age and sex may be determined fairly accurately from a clinical history of infection with or without such corroborative evidence as active lesions positive serologic tests or characteristic scars One may question the accuracy of diagnoses based upon such historical evidence alone especially among native peoples, but in one area in Jamaica where language difficulty was not a problem additional supporting evidence laboratory and clinical, confirmed the diagnoses in 97 per cent of persons giving a history of yaws of 10 years' duration or less[8] A study of the age distribution of yaws including latent cases in a group of 21 000 persons in rural Jamaica[80] showed that prevalence increased rapidly in childhood reaching a peak at about 10 to 15 years of age in males and about 10 years later in females after which there was a gradual decline in succeeding age groups (Table I)

TABLE I*

AGE AND SEX DISTRIBUTION OF YAWS IN JAMAICA

Age in Years	Percentage with Yaws — Males	Females
0–4	18.8	18.4
5–9	55.8	47.0
10–14	78.0	64.7
15–19	[illegible]6	65.8
20–24	[illegible]	71.0
25–29	74.8	6[illegible].0
40–45	66.2	61.2
50–55	63.7	59.4
60–65	63.8	54.6
75–79	55.4	54.5

* This table for selected age groups was condensed from material given in reference No 80

From Table I it can be seen that during the first five years of life there was essentially the same proportion of males and of females with yaws but that after this period prevalence increased more rapidly in males so that a higher peak (78 per cent) was reached at an earlier age than in females in whom the greatest prevalence (71 per cent) was attained 10 years later at 20 to 24 years of age After infancy yaws was more prevalent in males in all age groups and was found in about 57 per cent of 10 616 males and in about 50 per cent of 11 050 females of all ages

children in areas where prevalence is high and that where prevalence is lower infectious lesions will be found in older groups In the Jamaican studies[6] it was found that in one area, where about 60 per cent of the population had yaws nearly 90 per cent of all infectious lesions were found in children less than 15 years of age, while in another area where less than 50 per cent were infected less than 80 per cent of all infectious lesions occurred in children under 15 years of age

In this connection it is of interest that in a mountain province in the Philippines already referred to[7] about one half of the cases with yaws lesions were in adults and these lesions were practically restricted to areas around the mouth anus and genitalia The prevalence of yaws in the area was not stated but if there is a suppressive effect of cold on secondary yaws eruptions one would expect not only that the disease would tend to be acquired later in life because of the more intimate type of contact required with the restricted type of eruption but also that general prevalence would be less and this factor too would favor later infection

Hewer who studied treponematosis in the Southern Sudan stated the disease described as yaws has been prevalent since time immemorial it is characterized by a high though by no means absolute incidence of primary extra genital infections in childhood a spectacular framboesial eruption and reputed cure following a few injections of an arsenical preparation [8] He made detailed observations upon some 50 cases of treponematosis and general observations upon an additional thousand cases A differential diagnosis between yaws and syphilis based upon the usually accepted criteria was said to be impossible The population he examined lived in a swampy district about 1 400 feet above sea level where the annual rainfall amounted to 43 5 inches Among 246 cases only 99 or about 40 per cent were infected before 15 years of age while 60 per cent were infected later in life Primary genital lesions were noted in 54 patients 14 of whom were less than 15 years old No instance of a typical Hunterian chancre was found all primary lesions being diffuse granulomata and in women there were always condylomata Furthermore condylomata in the genital or axillary regions were the commonest manifestation of the disease Typical framboesiform papules circinate papular lesions plantar and palmar involvement with hyperkeratosis or ulcerating papular lesions were frequent also An estimate of the general prevalence of treponematosis in the area may be made from results of Kahn reactions on sera collected from 272 apparently healthy children and adults Thirty eight or about

as high as for males appears to be reached at an earlier age and to decline more slowly after the peak has been reached Some of the reasons for the variation in the rates at different ages and for the two sexes have been suggested in discussing prevalence There is a truly remarkable increase in infection rates in early infancy the rates for the second year being 5 to 7 times the rates for the first six months of life It would appear from this that, as soon as babies begin to crawl about and to walk and are less protected and coddled they begin to acquire yaws with ever increasing rapidity up to about 8 to 10 years of age, but after 10 years of age liability to infection declines possibly because of less group activities and hence less opportunity for exposure to yaws and possibly because of a lessening of the exuberant childhood vigor with consequently fewer cuts, scratches and abrasions Attack rates among females decline somewhat more slowly than among males after the peak has been reached and at 20 to 30 years of age there is little difference between the two sexes This may be explained by the fact that post-adolescent girls and young women remain at home to care for babies and small children who form the greatest reservoir of infectious yaws lesions

In comparing the observed prevalence of yaws in various age groups in Jamaica with the levels to be expected from a summation of attack rates at successive ages it was found that the observed prevalence for both males and females fell considerably below expected levels The difference between the two, which may be termed the deficit was found to increase rapidly up to 10 years of age and at a slower rate thereafter A reasonable explanation for the apparent decline in the level of infection in older age groups and for the deficit between observed and calculated levels is that evidences of infection (historical, clinical and serologic) gradually disappear and also that there is a higher mortality among persons infected with yaws with consequent longer survival of the non infected[10]

In regard to the age at infection with yaws, it appears that, as general prevalence increases the disease is acquired earlier in life In areas, where prevalence is high approaching saturation early infection is the rule while in areas with less yaws infection is more likely to be acquired later in life Since it is known that about 85 per cent of infectious types of yaws lesions occur within the first 5 years after the onset of the disease[11] and most of these during the first year or two it is to be expected that the great reservoir of infectious yaws will be in young

pected from this practice She answered that by this means their infants had the disorder slightly and recovered speedily, whereas by catching it at a later time of life the disease she said got into the bone "

During the past 150 years there have been numerous experiments on the direct transmission of yaws by inoculation Thomson[81] reported in 1819 that he had accidentally infected a slave with framboesia and later deliberately inoculated a child with infectious matter with the result that a generalized skin eruption presumably yaws, developed with seven weeks In 1848 Paulet[82] inoculated 14 negroes with secretions from yaws lesions and all developed the disease Since then there have been many other instances of successful transmission of yaws by direct transfer of virus

Apparent Absence of Congenital Yaws—The question of the transplacental infection of the fetus is one which has been the subject of much speculation and argument Hermans indicated that during the nineteenth century many observers expressed the belief that congenital yaws did occur and that some believed that in utero infection was a common occurrence[1] However where careful observations have been made on entire population groups heavily infected with yaws signs of congenital infection have been lacking In Jamaica where the natural evolution of the disease was studied by the Yaws Commission during the period 19, to 1937 a large rural population among whom the general yaws prevalence was about 50 per cent was kept under observation for a number of years Records were kept of births Most infants were examined during the first year of life, often during the first six months and in most instances the yaws status of the mothers was known Congenital yaws was never proven and in every case where the disease developed in a young infant it was traced to post natal infection from a known infectious case Infants born of mothers with serologic or other evidence of yaws who were examined during the first few months of life were found to be free of clinical sign of infection and serologic tests were negative Some of these infants were observed to develop yaws later and it evolved in a perfectly typical fashion with a single initial lesion followed in a period of time by a generalized skin eruption Chambers stated that in a total of more than 8 000 cases of yaws investigated in rural Jamaica no evidence was found that the disease caused congenital infection Physical findings and serologic tests made on infants less than six months old born of untreated yaws mothers were negative although in practically all instances the mothers had had yaws for many years He described one case however in which the

14 per cent of the sera give positive reactions, 20 per cent in adults and about 10 per cent in children

In this study both the general prevalence of treponematosis and the rainfall were relatively low when compared with other areas where yaws is prevalent and there was a relatively high proportion of new infections in adult life with presumably some venereal transmission It is possible that this is another example of treponematosis in the transitional stage between the almost universal exanthematous disease of childhood, as it appears in an environment most favorable for propagation and cutaneous evolution and the more suppressed pattern, occurring in less favorable surroundings in which surface lesions are less numerous transmission more difficult with infection tending to occur in older age groups

Manner of Transmission

The transmission of yaws requires transfer of viable spirochetes from an infected to a non infected individual and the implanation and multiplication or at least survival of organisms in the tissues of the new host It is generally believed that transmission is effected usually by direct bodily contact between persons with infectious skin lesions and others and that the virus is implanted on a pre existing break in the skin or mucosae There is some indication that indirect contact, infection by way of contaminated intermediate objects may occur and it is probable that insects may on occasion transmit the disease Although it has been suggested that trans placental transmission from infected mother to unborn child may take place there is no evidence that congenital yaws results even when the mother had typical florid framboesia during pregnancy

By Inoculation—That yaws is an inoculable disease has been known for a long time More than 150 years ago Bryan Edwards[19] observed that it was a common custom among natives of the Gold Coast to inoculate their children with yaws and he stated The following particulars were collected from some of my own Koromantyn negroes whose veracity I have no reason to doubt Clara who was brought to Jamaica the latter end of 1784 relates that she was born in a village near Anamaboo and that the natives of the Gold Coast give their children the yaws (a frightful disorder) by inoculation and she describes the manner of performing the operation by making an incision in the thigh and putting in some of the infectious matter I asked her what benefit they ex-

pected from this practice. She answered that by this means their infants had the disorder slightly and recovered speedily, whereas by catching it at a later time of life the disease, she said, got into the bone.

During the past 150 years there have been numerous experiments on the direct transmission of yaws by inoculation. Thomson reported in 1819 that he had accidentally infected a slave with framboesia and later deliberately inoculated a child with infectious matter with the result that a generalized skin eruption, presumably yaws, developed within seven weeks. In 1848 Paulet[11] inoculated 14 negroes with secretions from yaws lesions and all developed the disease. Since then there have been many other instances of successful transmission of yaws by direct transfer of virus.

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mother became infected during the late months of pregnancy and had active disease before and after the birth of the child The child showed no signs of yaws and had negative serologic tests during its first year of life[8] Similar cases have been observed in other yaws areas of the world and it is certain that infection of the fetus occurs only rarely, if at all

In this respect yaws behaves in very different manner from adult, civilized syphilis It is well known that infants born of mothers with untreated syphilis of less than 2 years duration very commonly are syphilitic It is stated that in about 80 per cent of such pregnancies the fetus is infected[5] resulting either in miscarriage or in the birth of a premature or full term living or dead infant with congenital syphilis However tribal syphilis such as bejel which is usually the result of childhood infection is said to behave like yaws is the rarity of congenital infection Hudson wrote one may go farther and state that when syphilis is, like yaws a community disease acquired in childhood and virtually untreated it resembles yaws in the rarity of congenital transmission"[36]

The reasons for the differences in the frequency of fetal infection among the various patterns of treponematosis are not clearly understood One explanation which is offered is that since infection of the fetus occurs primarily during the first few years of disease and only rarely after that time congenital infection would not be expected in the primitive patterns of treponematosis acquired in childhood because the disease would have passed into the later stages by the time the women were old enough to bear children However the duration of infection does not appear to be the sole determining factor, because in many cases mothers with early active untreated yaws have given birth to healthy babies and no authentic cases of congenitally infected infants have been reported

Another explanation is suggested by the differences in the clinical patterns of treponematosis In yaws there is usually an early, violent reaction to infection with widespread hypertrophic granulomatous skin lesions and extensive involvement of bones while in adult syphilis the early skin lesions are relatively insignificant and mild as a rule This suggests that strains of *T pertenue* have a peculiar affinity for certain tissues particularly those of the skin and bones where conditions may be more favorable for their survival and reproduction than in other structures such as the placenta Because of continuous reproduction in the tissues of the integument where environmental factors of moisture and warmth favor such localization it is conceivable that the surviving

organisms will be mutant strains which are better able to survive and reproduce in these structures when transplanted to a new host and that the placenta among other tissues offers a less favorable medium for growth. It is possible that the temperature of the tissues is a factor influencing localization and that strains of organisms which have become adapted to the slightly lower temperature of the outer layers of the skin find the higher temperatures of other tissues including the placenta, relatively unfavorable.

In this connection Dubos cited evidence that *T. pallidum* from the inguinal and popliteal lymph nodes of experimentally infected rabbits and guinea pigs and from the spleen and brains of infected mice are more resistant to heat than those found in skin lesions and furthermore that treponemes found in human lymph nodes are resistant to a temperature of 4 °C for one to three hours while those found in skin lesions are killed when kept at a temperature of 41°C for two hours. He stated "it is evident therefore that strains of pathogenic microorganisms differ in their optimal temperature for survival and multiplication and that this difference can be of some significance in affecting their pathogenicity for a given host."

It is known that the outer layers of the human body are colder than deeper structures unless environmental temperatures are extremely high. Pennes who measured temperatures of the resting human forearm stated that surface temperatures ranged from 31°C to 35°C, while temperatures at a depth of 3.5 cm were about 36.8°C.[87] Cowdry stated that the skin functions at temperatures which are about 5°C lower than the mucosae of the rectum and vagina.[88] Wiggers reported that the temperature of the surface of the body is 5°C lower than internal temperatures that rectal temperatures are about 0.5°C higher than mouth temperatures that liver temperatures are higher than rectal by as much as 1°C and that aortic blood is cooler than the liver by 0. to 0.5°C.[89]

T. pallidum, in contrast to *T. pertenue*, appear to be better adapted to life in tissues such as those of the central nervous system blood vessels and placenta where temperatures are higher than those of the skin. It may be that the level of metabolic processes has an effect in determining parasite localization and that the metabolism is generally lower in tissues where *T. pertenue* tends to localize than it is in tissue favored by syphilis.

The apparent tissue selectivity of strains of treponemata is believed to be a changeable temporary quality because of the alterations of the

clinical pattern which develop under varying environmental conditions. It has been suggested that with less warmth and moisture the eruptive secondary stage of yaws becomes less profuse, drier and more localized about warm, moist parts of the body. Transmission is affected adversely and tends to occur later in life not only because of the altered character of the eruption but also because prevalence is less, with a resulting smaller risk of infection. With successive transfers from person to person under conditions where the pattern of host response is altered, the parasite may become adapted to a more "inward" way of life with the development of strains which find optimal conditions for reproduction in tissues other than the skin. It is probable that the process is reversible and that the adult inward pattern would under suitable environmental conditions gradually revert to the more primitive, exanthematous pattern. The time required for such alterations, if indeed they do occur, is not known. Probably centuries or possibly only a few host to host transfers might be required. But for whatever reasons it appears certain that in yaws as it occurs naturally in a favorable environment the placenta and fetus afford less suitable sites for multiplication of its strain of spirochetes than do other tissues and congenital yaws is a rarity.

By Insects.—During the past few centuries transmission of yaws has been attributed repeatedly to insects, especially certain species of small flies and it is probable that at times infection results from transfer of organisms by various insects acting as purely mechanical vectors. As long ago as 1587 Carlos Franco stated that in Brazil yaws was conveyed from man to man by small flies which feed upon the sores and then settle on skin abrasions of the healthy.[13] Hermans quoted observation extending back to 1770 in support of insect transmission, many referring to a special small fly called the "yaws fly."[1] In 1817 John Williamson stated that the disease "may be communicated from flies alighting from the yawey patient."[0] About the same time Thomas Dancer wrote "sometimes the yaws begin with a common ulcer which has probably been inoculated by a fly."[1] In 1907 Castellani stated "in my opinion, there can be little doubt that in certain cases insects may carry the disease. It is very noticeable that flies eagerly crowd on open sores of yaws patients. The yaws ulcerations become covered with flies sucking with avidity the secretions which they may afterward deposit on ordinary ulcers of other patients." To test this hypothesis he carried out a series of experiments in which ordinary house flies, *Musca domestica*, were fed on secretions from yaws lesions in humans and then

placed over scarified areas on the eyebrows of monkeys T pertenue having previously been demonstrated in the mouth parts of some of the flies Some of the monkeys later developed ulcerated papular lesions at the sites of inoculation and treponemes were found in material from the lesions[57]

Nicholls in an interesting summary of his observations on yaws in St Lucia during the years 188--1910 reported that a small fly *Hippelates flavipes*, probably was of great importance as a vector of yaws[90] The Annual Report for the Public Health Service of Haiti for 19 9 implicated the same fly as an important factor in the transmission of yaws[1] In 1934 Thomson and Lamborn published a report on the possible role of non biting hematophagous flies particularly *Musca spectanda*, in the spread of yaws They observed that in Nyasaland this fly concentrated on man and attacked persistently and with great determination scratches wounds open sores yaws nodules and greedily drinks to repletion blood serum or secretions They noted that soon after feeding the flies began to pass liquid excreta and they were able to observe actively motile *T pertenue* in excreta passed by flies for an hour after they had been fed on open yaws lesions From this it was concluded that this species of fly could easily deposit *T pertenue* on cuts and abrasions after feeding on yaws lesions[9] Lamborn recorded the successful transmission of yaws to a native volunteer by flies *Musca sorbens* This species after feeding upon yaws sores regurgitates the treponemata in its vomit drop[93]

Other insects have been implicated as possible vectors and a group of Indian workers suggested that the red ant may play some part in the spread of yaws[94] This possibility had been mentioned earlier by Castellani who noted that ants were found occasionally on yaws lesions as well as on non specific ulcerations[17]

Small flies of the genus *Hippelates* sometimes called eye gnats are the insects mainly incriminated in the West Indies Kumm and co workers found that *H pallipes* (the same as *H flavipes* mentioned by Nicholls[90]) feed on yaws lesions in enormous numbers preferably on lesions of the lower extremities These flies may take in large numbers of *T pertenue* some of which may be regurgitated later in vomit drops Actively motile treponemes were found in the esophageal diverticulum for more than seven hours after feeding[54] Later Kumm and Turner demonstrated by feeding experiments that yaws can be transmitted from man to rabbits by *H pallipes*, and they stated that there was every reason to believe that the transfer from man to man may occur

clinical pattern which develop under varying environmental conditions. It has been suggested that with less warmth and moisture the eruptive secondary stage of yaws becomes less profuse, drier and more localized about warm, moist parts of the body. Transmission is affected adversely and tends to occur later in life not only because of the altered character of the eruption but also because prevalence is less, with a resulting smaller risk of infection. With successive transfers from person to person under conditions where the pattern of host response is altered the parasite may become adapted to a more "inward" way of life with the development of strains which find optimal conditions for reproduction in tissues other than the skin. It is probable that the process is reversible and that the adult "inward" pattern would under suitable environmental conditions gradually revert to the more primitive exanthematous pattern. The time required for such alterations, if indeed they do occur, is not known. Probably centuries or possibly only a few host to host transfers might be required. But for whatever reasons it appears certain that in yaws as it occurs naturally in a favorable environment the placenta and fetus afford less suitable sites for multiplication of its strain of spirochetes than do other tissues and congenital yaws is a rarity.

By Insects.—During the past few centuries transmission of yaws has been attributed repeatedly to insects, especially certain species of small flies and it is probable that at times infection results from transfer of organisms by various insects acting as purely mechanical vectors. As long ago as 1587 Carlos Franco stated that in Brazil yaws was conveyed from man to man by small flies which feed upon the sores and then settle on skin abrasions of the healthy.[13] Hermans quoted observation extending back to 1770 in support of insect transmission, many referring to a special small fly called the "yaws fly." In 1817 John Williamson stated that the disease "may be communicated from flies alighting from the yawey patient."[6] About the same time Thomas Dancer wrote "sometimes the yaws begin with a common ulcer which has probably been inoculated by a fly." In 1907 Castellani stated, "in my opinion there can be little doubt that in certain cases insects may carry the disease. It is very noticeable that flies eagerly crowd on open sores of yaws patients. The yaws ulcerations become covered with flies sucking with avidity the secretions, which they may afterward deposit on ordinary ulcers of other patients." To test this hypothesis he carried out a series of experiments in which ordinary house flies, *Musca domestica*, were fed on secretions from yaws lesions in humans and then

who lived in homes adjacent to those of the old case, and there was close association at play and in the homes In about [illegible] per cent of new cases no likely source could be traced [illegible] In several instances the location of infectious lesions on the donor and of primary lesions on the recipient of *T pertenue* and the history of close personal contact provided overwhelming evidence in support of direct transfer In one such case a mother who said she had never had yaws and whose serologic tests and physical examination supported her statement appeared in the clinic with her suckling infant who had florid framboesiomata about the mouth About two months later the mother was seen again this time with a darkfield positive frambocsiform lesion on one breast, most surely a primary yaws lesions In another instance a 16 year old girl brought her yawey baby brother to the clinic carrying him in her arms in such a way that the baby s face which was covered with hypertrophic yaws lesions rested against her right upper arm Examination showed that the sister was free from yaws at that time but when seen about 3 months later examination revealed over the right upper arm what was undoubtedly a primary yaws lesion which had been present for a few weeks and early generalized yaws lesions Many other similar cases might be described in which direct transfer of infectious material was accomplished by personal contact

The fact that a close spatial and a suitable temporal association can be established between a new case of yaws and another with infectious lesions does not of course contribute final proof that the disease was communicated directly from one to the other Flies or other insects might carry infection between individuals living in the same or in nearby household but if this were quantitatively an important way of transmission one would expect that insect transmission would also be occurring in the market place in schools in churches and in shops and that there would be a greater geographic scattering of new cases rather than the observed close grouping of new cases about a suspected source case Furthermore if consideration is given to the way of life among most yaws stricken populations the lack of cleanliness the scanty clothing the crowding and the general disregard of leg ulcers then it becomes apparent that frequent bodily contacts between persons of all ages sexes and states of health are inevitable If one infectious case of yaws is introduced into a family of children the disease inevitably will be passed from one to the other over a period of months until all have been infected unless the chain is broken by treatment or isolation It was a common experience in Jamaica to find a household with several children,

in the same way In a study of the epidemiology of yaws in Jamaica it was found that *H pallipes* were present in large numbers everywhere that the incidence of yaws was high However, the same species was common in certain other localities where yaws was seen rarely but where the vegetation was of the dense jungle type, and where rainfall was high It could not be decided whether the distribution of *H pallipes* in Jamaica influenced the distribution of yaws, or whether both were affected by the same environmental factors causing their distribution to coincide [9]

It is probable that insects especially flies which feed upon human wounds abrasions and open sores of any kind may play a part in determining the prevalence and distribution of yaws but it is unlikely that their role is an important or deciding one Yaws transmission would doubtless go on without interruption in the absence of flies

By Personal Contact —Direct and indirect evidence is in favor of personal contact as the usual way of infection physical contact between the bodies of persons with infectious yaws lesions and others without yaws Since the disease is primarily one of childhood in most areas where its prevalence is great, contact transmission is usually non-venereal Transmission may take place during sexual contact particularly where the disease is common in older age groups and where because of environmental conditions the early generalization of lesions is suppressed and restricted to the genital peri anal or peri oral regions of the body

In most areas where yaws prevails the sources of infection are so numerous that it is impossible to trace with certainty the origin of new cases However in a large area of rural Jamaica where intensive treatment methods had greatly reduced the sources of infection and where frequent follow-up observations permitted the early detection of most new infections it was usually possible to find a patient with infectious yaws as the logical source of infection and to show a close association between the new case and the suspected source In most instances there was a definite history of injury at the site where the initial lesion later appeared In a study of the circumstances surrounding the development of 270 new cases of yaws ample opportunity for recent contact with persons known to have had infectious yaws lesions was demonstrated in 75 per cent In the majority the old and new cases were members of the same household and in about 15 per cent the new cases were persons who had slept in the same bed (or on the floor) with the presumed source case In a number of instances the new cases were in children

provided by clinical and epidemiological observations on the disease in humans and by studies of the infection in experimental animals. The accumulated evidence indicates a slowly developing resistance to infection which increases gradually over months and years until a relatively solid immunity is built up. Resistance is generally greater to homologous than to heterologous strains of organisms but a serviceable cross immunity between spirochetes producing different clinical patterns also results.

It has been suspected for a long time that infection with yaws protects against subsequent attacks of the disease. Edwards referred to the custom "which prevailed among West African tribes in the 18th century, of inoculating children with yaws to prevent them from acquiring the disease later in life"[19] Williamson stated that "the yaws like the small pox can be taken only once during life." Hermans quoted numerous observations and experiments which indicate that immunity to yaws develops as a result of infection[1] The Jamaican negro believes that treatment for yaws should not be given until the disease is "well ripe" that is until wide spread generalization has developed in order to prevent later lesions or re infection. From careful observations of the natural evolution of the disease it is obvious that resistance to the invading spirochetes gradually develops. In early stages there is a wide spread dissemination of organisms with manifest extensive lesions of skin and bones. After several months the early reaction subsides and a period of latency follows which is interrupted from time to time by relapsing lesions. These are less extensive than during the early months of infection and tend more and more to be the late destructive type in which spirochetes are so few in number that they cannot be found by ordinary methods. If no resistance were built up one would expect an indefinite continuation of the early type of lesions unless specific treatment was given. In areas where yaws is prevalent and most of the adult population have already had the disease new infections are seldom found among adults partly because they are less liable to infection but largely because of immunity conferred by infections acquired in childhood.

Immunity resulting from infection of man or experimental animals with treponemes has commonly been measured by the success or failure to produce obvious lesions by subsequent reinoculation with either the same or with other strains of organisms but recently carefully controlled quantitative experiments have revealed that immunity to treponemes is a relative state which depends upon the duration of the first

one or more of them with infectious yaws lesions, sharing the same bed or the same corner of the floor

The frequency of the appearance of the primary yaws on the lower legs feet or ankles is additional presumptive evidence of direct transfer of infection The site of the initial lesion probably is determined largely by the greater frequency of injuries of the lower extremities than of other parts of the body and because the lower legs and feet are the anatomical area most apt to come into direct contact with the legs and feet of another particularly in children who usually sleep several in a group unclothed except for a short shirt covering the upper part of the body

It is possible that infection may be accomplished indirectly through communal use of various contaminated objects such as dishes, drinking cups eating utensils or clothing Possibly infants just beginning to crawl may become infected by contact with infectious material deposited on the floor by a person with an open plantar papule Plantar papules because of their location are subject to repeated trauma which may destroy the protective crust and allow free discharge of serum teeming with spirochetes Viable organisms may survive apart from the human host for considerable periods of time providing there is adequate moisture a suitable temperature and protection from sunlight

Immunity

The term immunity has a wide range of meaning It is used in connection with many diverse manifestations of reaction between parasite and host between which there is usually a fluctuating unstable equilibrium During the early period of invasion the parasite may flourish and stimulate marked cellular and other reactions in the host, which may result in a gradual suppression or elimination of the invading organisms and a decline or disappearance of signs of host reaction For the present purpose immunity may be defined as resistance to invasion or alteration in the pattern of host reaction to treponemes resulting from infection with the same or other strains of spirochetes There is probably no innate immunity in man to treponemata infection being followed by a pattern of reaction which is fairly constant for one strain of organisms but which varies in some respects with the age sex and racial characteristics of the host and with the total environment

Information concerning immunity in treponematous infections is

diseases In 1923 in the Philippines Sellards and Goodpasture[101] attempted to reinfect yaws patients by applying to scarified skin areas material containing a few *T pertenue* obtained from typical yaws papules Three patients with primary and generalized yaws lesions had had the disease for two four and five months In two of them the scarifications healed promptly and no new lesions were noted at the sites of inoculation during a period of 6 weeks In one case a granulomatous lesion developed which promptly regressed spontaneously In two additional patients with untreated yaws of more than 10 years duration and with plantar hyperkeratosis and positive serologic tests similar inoculations produced only a transient papillary eruption at the site of the scarification Four other patients who had had early yaws lesions for periods varying from 3 months to two years were treated with neosalvarsan with healing of lesions Several months later these patients were reinoculated by inserting fragments of tissue from a yaws papule into incisions in the skin One patient whose initial infection was of 3 months duration and whose Wassermann reaction was negative at the time of reinoculation subsequently developed granulomata at the inoculation site and scattered discrete papules over the body In another patient who had had yaws for 8 months before treatment a typical granulamatous yaws lesion developed at the inoculation site after about two months but this healed slowly without the appearance of generalized skin lesions Both these patients were given further treatment In the other two patients whose initial infection had lasted for one and for two years only slight atypical transient reactions limited to the inoculation area resulted

From these observations the authors concluded that a measurable degree of immunity develops in yaws immunity which persists even after the disease apparently has been cured by treatment However, the interpretation of the results is difficult particularly in the light of what is known of the quantitative aspects of resistance to reinfection In the first place the size of the challenge inoculum was not known although it was stated that few treponemata were seen in stained preparations Furthermore in patients with active yaws it would be difficult if not impossible to decide if any additional lesions which might appear were caused by decedents of treponemes present in the inoculum or by those already present in the body However it may be assumed that some resistance to reinfection did result from the naturally acquired disease

The 4 patients who were inoculated with yaws some time after naturally acquired infections had been treated were studied again more

or immunizing infection and upon other factors, and which may be measured by the number of organisms required to produce reinfection or superinfection. Because of this newer knowledge many previous observations must be re-evaluated and new conclusions drawn.

Magnuson, Rosenau and Clark investigated the quantitative aspects of immunity in rabbits which resulted from infection with the Nichols strain of *T. pallidum* under carefully standardized experimental conditions. The first infections were produced either by intratesticular or by intracutaneous inoculation of several million *T. pallidum*. After 3, 6, 12 or 24 weeks the infection was treated with curative doses of mapharsen or of penicillin and 6 weeks later the immunity, which had developed, was challenged by re-inoculating with a known number of *T. pallidum*. It was found that the second or challenge inoculation resulted in three types of response: (1) in manifest symptomatic disease, (2) in asymptomatic infection with no detectable lesions or (3) in no reinfection. The type of response to re-inoculation was found to vary with the duration of the first infection and the number of organisms in the challenge inoculum. As the duration of the original infection increased, progressively greater numbers of organisms were required to produce the same response. A small but demonstrable degree of immunity had developed after three weeks. This increased rapidly so that by the 24th week it was of such a degree that it was almost impossible to inoculate large enough numbers of *T. pallidum* to produce symptomatic reinfection.[99] In contrast, it is known that one or two *T. pallidum* will produce symptomatic infection in practically all rabbits not previously infected with treponemes. Magnuson points out that although much of the information on acquired immunity in experimental infections in animals may not be directly applicable to man, the clinical features of the human disease are remarkably similar to findings in experimental animals and that many of our basic concepts of acquired immunity have had to rest upon evidence gathered from studies in animals.[100] One may question the validity of comparisons between syphilis in experimental animals and yaws in man, but because the basic pattern of reaction of certain animals and humans to spirochetes of syphilis or yaws are similar, it is believed that such comparisons are pertinent.

Inoculation Experiments.—In an attempt to assess the degree of specific or reciprocal immunity in yaws and syphilis many inoculation experiments have been performed. A brief review of some of them will indicate the extent of our knowledge of immunity in treponematous

diseases In 1933 in the Philippines Sellards and Goodpasture[101] attempted to reinfect yaws patients by applying to scarified skin areas material containing a few *T pertenue* obtained from typical yaws papules Three patients with primary and generalized yaws lesions had had the disease for two four and five months In two of them the scarifications healed promptly and no new lesions were noted at the sites of inoculation during a period of 6 weeks In one case a granulamatous lesion developed which promptly regressed spontaneously In two additional patients with untreated yaws of more than 10 years duration and with plantar hyperkeratosis and positive serologic tests similar inoculations produced only a transient papillary eruption at the site of the scarification Four other patients who had had early yaws lesions for periods varying from 3 months to two years were treated with neosalvarsan with healing of lesions Several months later these patients were reinocuated by inserting fragments of tissue from a yaws papule into incisions in the skin One patient whose initial infection was of 3 months duration and whose Wassermann reaction was negative at the time of reinoculation subsequently developed granulomata at the inoculation site and scattered discrete papules over the body In another patient who had had yaws for 8 months before treatment a typical granulamatous yaws lesion developed at the inoculation site after about two months but this healed slowly without the appearance of generalized skin lesions Both these patients were given further treatment In the other two patients whose initial infection had lasted for one and for two years, only slight atypical transient reactions limited to the inoculation area resulted

From these observations the authors concluded that a measurable degree of immunity develops in yaws immunity which persists even after the disease apparently has been cured by treatment However the interpretation of the results is difficult particularly in the light of what is known of the quantitative aspects of resistance to reinfection In the first place the size of the challenge inoculum was not known although it was stated that few treponemata were seen in stained preparations Furthermore in patients with active yaws it would be difficult if not impossible to decide if any additional lesions which might appear were caused by decedents of treponemes present in the inoculum or by those already present in the body However it may be assumed that some resistance to reinfection did result from the naturally acquired disease

The 4 patients who were inoculated with yaws some time after naturally acquired infections had been treated were studied again more

than two years later when their susceptibility to yaws was tested again.[102] At this time these patients were free from any clinical signs of yaws and the Wassermann reactions were negative. They were reinoculated by implanting pieces of tissue from yaws papules. Only one developed a typical granuloma. One of the others developed no lesion, although the Wassermann reaction was later found to be positive. Each of the other two developed an atypical abortive type of local reaction, in one the Wassermann reaction became positive, while in the other it remained negative. The patient who responded to this second reinoculation with typical yaws lesions, although only after what was probably a prolonged incubation period, was the same one whose initial infection had persisted for only [illegible] months before treatment was given. He had responded to the first reinoculation with characteristic yaws lesions for which he was promptly given more treatment.

Sellards, Lacy and Schobl[1] inoculated 6 volunteers, previously free of yaws, by the implantation into skin incisions of pieces of yaws tissue rich in treponemes. In 5 patients typical granulamatous lesions showing *T. pertenue* developed at the inoculation sites three and one-half to four weeks later. In the sixth only an atypical abortive papule appeared. Four, five and six weeks after the first inoculation, auto-inoculations were made in the first five patients by implanting a fragment of their own primary yaws lesions into skin incisions. The sixth was reinoculated with material from one of the others. The five who developed primary yaws following the first inoculations developed similar lesions at the sites of the second inoculation with incubation periods of three and one half to six weeks. Although the sixth patient failed to develop a lesion at the site of the second inoculation, he and all the others developed scattered secondary lesions which appeared in ten or eleven weeks in the first five and in fifteen and a half weeks in the sixth. These results indicate that superinfection is readily achieved in the early weeks or months of yaws, but they give little evidence for or against the development of immunity. It must be inferred that the challenge inocula contained *T. pertenue* in numbers far in excess of those necessary to overcome the low degree of resistance which might have developed during the first four to six weeks of infection.

Turner conducted a series of inoculation experiments in yaws patients in Jamaica. Eighteen patients who had had yaws for periods varying from one week to as long as seven years and who nevertheless exhibited infectious yaws lesions were inoculated intradermally with serum containing *T. pertenue* from their own lesions. With one excep-

tion the results of these homologous inoculations were negative in that new lesions failed to develop at the site of inoculation In 67 additional patients with yaws of varying duration and clinical manifestations intradermal inoculations were performed with 0 1 to 0 2 c c of infectious material from other patients In 30 patients in whom the duration of the first infection was less than 3 years lesions appeared at the site of inoculation in 73 per cent while in 37 patients with yaws of more than 3 years duration only 29 per cent responded with lesions It was concluded that resistance to auto-inoculation appears early in the course of yaws but that immunity to heterologous strains develops slowly, so that during the first 3 years reinoculation may be followed by modified or abortive lesions, while after a period of 10 years the majority of yaws infected persons are refractory to reinoculation[104] However, in Turner's experiments as in those previously described it is probable that the number of *T pertenue* in the inocula was many hundred or even thousands of times greater than would be required to produce yaws in a completely non-immune person It is likely that if only a few spirochetes had been inoculated considerable resistance to the production of manifest lesions would have been shown in the majority of persons with yaws of even less than 3 years Furthermore how frequently asymptomatic infection was produced in those failing to exhibit new lesions after reinoculation is not known

Animal Experiments —Soon after the announcement of the discovery of *T pertenue* as the cause of yaws a search was started for susceptible laboratory animals in which the results of infection might be studied under controlled conditions In 1906 monkeys were successfully inoculated with yaws and soon successful transfer from humans to the higher apes and to several species of monkey was reported[10] In 1910 Nichols infected rabbits with yaws spirochetes and compared the resulting lesions with those produced by the spirochetes of syphilis[108] During the past forty years there has accumulated a vast amount of experimental data on yaws and syphilis in animals which may have a direct bearing both on the clinical course and on immunity in the two conditions in humans The results of only a few of the more pertinent observations will be mentioned

Matsumoto has summarized the results of studies on experimental spirochetosis which were made by him and his co workers at the Institute of Dermatology and Syphilology of the Imperial University of Kyoto[51] In one series of experiments rabbits were inoculated with *T pertenue* either by implanting bits of yaws tissue into the scrotal skin or by

injection of virus emulsion into the testes After varying periods of time the animals were reinoculated in the same manner It was found that grossly demonstrable lesions occurred regularly when reinoculation was performed during the incubation period and also when the primary lesion was still present a period of time ranging from 35 to 123 days after the first infection When reinoculations were made 146 to 455 days after the first inoculations and during the first 7 months after the appearance of the original primary lesion symptomatic superinfection as shown by the development of obvious lesions, resulted in the majority of animals When reinoculations were performed later manifest superinfection did not occur Stated in another way obvious reinfection always resulted when reinoculation was performed within 2½ months after the appearance of the first lesion while after a lapse of 8 months the result was consistently negative It was noted that lesions produced by reinoculation were smaller and of relatively feeble development" as compared with the original primary lesions These results indicate the development of a slowly acquired resistance to superinfection with *T pertenue*, but unfortunately these experiments do not measure the degree and time of appearance of immunity because the size of the challenge inoculum probably was sufficiently great to overcome early, slight resistance

In another group of rabbits with symptomatic yaws presumably curative treatment with arsphenamine was given at varying periods after infection and 35 to 60 days following treatment the animals were reinoculated Manifest reinfection occurred in all rabbits even though the first infection before cure had persisted for 8 to 10 months However the lesions resulting from reinfection were generally milder than those of the first infection" These observations which suggest that the immunity produced by the first infection is somehow destroyed or modified by treatment, are in direct contrast to the results in experimental syphilis in which it was found to be almost impossible to produce symptomatic reinfection in rabbits with a homologous strain of *T pallidum*, if the first infection had persisted as long as 12 months before curative therapy Experimental conditions were not the same in the yaws and in the syphilis studies

In the studies reported by Matsumoto the numbers of organisms in the original or challenge inocula although presumably large were not known Furthermore he did not state whether the same or different strains of *T pertenue* were employed in reinfection experiments In

the syphilis studies the numbers of organisms in inocula were carefully quantitated and homologous strains were used for reinoculation

Turner who reinoculated rabbits with heterologous strains of *T pertenue* six months after the first infection concluded that a substantial degree of immunity had developed[107]

Schobl's[54] observations on experimental yaws in Philippine monkeys also illustrate the development of immunity In monkeys local yaws lesions appeared regularly at the site of intradermal inoculations When repeated reinoculations were given the initial lesion persisted and in some cases generalized papular lesions very similar to framboesiform lesions in humans appeared Reinoculations during the first five months after the appearance of the first lesion resulted in local lesions in the inoculation area similar to those produced by the first infection during the sixth month the majority and from the seventh to the fourteenth month all monkeys were resistant to reinoculation in that no new lesions developed In another group of similarly infected monkeys in which treatment with neoarsphenamine was given after the first lesion had been present for periods varying from 1 to 18 months subsequently reinfection was attempted It was found that when animals were treated during the first two months of the first infection they remained susceptible to reinoculation and developed a local yaw when reinoculated within seven months of the first inoculation but the animals that received treatment later than the third month were resistant to reinoculation during the seventh months or at later periods Schobl believed that repeated superinfection had no apparent effect on the early development of immunity but that the generalization of yaws hastened the production of resistance to superinfection

All evidence indicates that immunity to yaws is built up slowly During the first several months of infection superinfection is possible but as the duration of the infection increases the resistance to the same and to different strains of *T pertenue* increases until no obvious new lesions are produced by reinoculation either an asymptomatic infection results or the immunity may be so great that reinfection does not occur with the size of the challenge inocula ordinarily used Experimental results further suggest that treatment given early in the first infection interferes with the development of resistance to subsequent infection but that treatment given later has little effect The solidity of the immune state probably is a result of the product of the duration and of the intensity of infection and is a relative quantitative phenomenon An early widespread violent reaction to infection indicates massive

injection of virus emulsion into the testes After varying periods of time the animals were reinoculated in the same manner It was found that grossly demonstrable lesions occurred regularly when reinoculation was performed during the incubation period and also when the primary lesion was still present a period of time ranging from 35 to 123 days after the first infection When reinoculations were made 146 to 455 days after the first inoculations and during the first 7 months after the appearance of the original primary lesion symptomatic superinfection as shown by the development of obvious lesions resulted in the majority of animals When reinoculations were performed later manifest superinfection did not occur Stated in another way obvious reinfection always resulted when reinoculation was performed within 2½ months after the appearance of the first lesion while after a lapse of 8 months the result was consistently negative It was noted that lesions produced by reinoculation were smaller and of relatively "feeble development" as compared with the original primary lesions These results indicate the development of a slowly acquired resistance to superinfection with *T pertenue*, but unfortunately these experiments do not measure the degree and time of appearance of immunity because the size of the challenge inoculum probably was sufficiently great to overcome early, slight resistance

In another group of rabbits with symptomatic yaws presumably curative treatment with arsphenamine was given at varying periods after infection and 35 to 60 days following treatment the animals were reinoculated Manifest reinfection occurred in all rabbits even though the first infection before cure had persisted for 8 to 20 months However, the lesions resulting from reinfection were generally milder than those of the first infection' These observations, which suggest that the immunity produced by the first infection is somehow destroyed or modified by treatment are in direct contrast to the results in experimental syphilis in which it was found to be almost impossible to produce symptomatic reinfection in rabbits with a homologous strain of *T pallidum*, if the first infection had persisted as long as 12 months before curative therapy Experimental conditions were not the same in the yaws and in the syphilis studies

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are generally mutually exclusive. In areas where the syphilis pattern is prevalent yaws usually is absent while syphilis is found rarely where the yaws pattern prevails, even where the two areas are in close communication with ample opportunity for exchange of the two patterns of disease. This was a striking finding in Jamaica where more than 50 per cent of a rural population of 4,500 people had yaws, while in only 22 or 0.5 per cent the diagnosis of syphilis seemed reasonable.[3] On the other hand, in one large city of Jamaica syphilis was seen frequently but yaws cases were very rare and usually were imported to the city from rural yaws areas. In a survey for syphilis among 1,100 school children in Kingston, Whitbourne and Saunders found that 30 or 2.7 per cent probably had yaws acquired elsewhere.[109] This is in marked contrast to the rural yaws area of Jamaica, where about 75 per cent of children of school age had evidence of yaws and congenital syphilis was not seen in a single case. Harper[110] stated that in Fiji yaws had been prevalent for a long time but that syphilis did not prevail, even though it had been constantly introduced into the area since the coming of foreigners. Throughout most of the tropical world it is found that either yaws or syphilis may be prevalent in any area but not both. There are a few exceptions to this general rule and in some regions where environmental factors which influence the development of yaws syndrome are borderline, yaws and syphilis patterns are found side by side, although usually one type predominates. Such an area is that in the Southern Sudan described by Hewer, who found that many cases of treponematosis could not be labelled neatly as either yaws or syphilis.[4]

The apparent exclusiveness of yaws and syphilis may result partly from epidemiologic and environmental factors such as the social and economic level, poverty or wealth, personal habits, cleanliness or filth and climate, which favor the propagation and development of one type over the other, and partly from the immunity one pattern of infection provides against the other. The chance that a person with infectious syphilis introduced into a yaws area will transmit syphilis to other adults is small because most potential sexual partners have already had yaws for many years and therefore, if our assumption is correct, have sufficient resistance to syphilis to prevent infection with *T. pallidum*. Therefore the syphilis pattern is confined and cannot spread. An alternate possibility is that syphilis so introduced may spread through the relatively small fraction of the population which possesses no immunity as the result of previous experience with treponemata, but that the cases which develop are either not properly classified or the pattern of infec-

numbers of treponemes in the tissues which serve to stimulate an antibody response It is conceivable that a widespread infection of short duration will stimulate as great a resistance to treponemes as a more restricted infection persisting for a longer time

The evolution of resistance to yaws spirochetes in experimental animals and in some respects the disease pattern itself, is strikingly similar to that observed in human infections or deduced from epidemiologic and other evidence In both there is the slow development of immunity which increases with the duration of infection at least up to a certain point In both there is a relatively long incubation period of several weeks or months followed by a single granulomatous lesion and later by multiple widespread generalized lesions which usually disappear spontaneously after several months as resistance to the invading organisms is built up Late destructive ulcerative lesions are common in human yaws and similar manifestations have been produced in monkeys[104] by superinfection In early lesions in man or experimental animals treponemata are found in abundance but are present in small numbers if at all in the ulcerative late lesions

Reciprocal Immunity in Yaws and Syphilis—Confusion has arisen concerning cross immunity between yaws and syphilis largely because of conclusions drawn from a limited number of observations but also because of the frequent failure to appreciate the fact that the immune state is relative rather than absolute There have been reports of apparent infection of syphilitics with yaws or of yaws patients with syphilis These have been interpreted as evidence of lack of cross-immunity without taking into consideration either the quantitative aspects of resistance or the fact that reinfection with syphilis after syphilis or of yaws after yaws is not an uncommon occurrence provided that in either disease treatment of the original infection was instituted early On the other hand there have been reports of apparent failure to superimpose infection with yaws upon syphilis or syphilis upon yaws which have been interpreted as evidence of immunity, but again quantitative factors have not been controlled However the preponderance of evidence epidemiologic clinical and experimental favors the opinion that a reciprocal immunity does develop as a result of infection and that following infection with *T pertenue* the resistance to *T pallidum* probably is weaker than the resistance to either *T pertenue* or to *T pallidum* in infection with *T pallidum*

There is considerable epidemiologic evidence of cross immunity between yaws and syphilis It has been stated that the two conditions

from a case of syphilis. An alternative is that the patient was cured of his yaws and contracted a new infection with a venereal strain of spirochetes and all his new lesions were syphilis. Hypertrophic "framboesiform" lesions in cases of syphilis in dark-skinned races are not rare even in temperate or cold climates. In short, proof that yaws fails to protect against syphilis cannot be adduced from such case reports.

Chambers believed that there was a certain amount of reciprocal immunity between yaws and syphilis but that the immunity was not absolute. He cited as proof five cases in which syphilis was apparently contracted many years after infection with yaws which had remained untreated[4].

It is probable that many persons who have had yaws, which has either been treated or which has followed its natural course and progressed to latency in the absence of treatment, may be reinfected with yaws or with syphilis with the production of manifest disease. Likewise reinfection with syphilis is not uncommon following curative therapy early in the disease and occasional cases of reinfection late in the disease are reported. Peabody and Webster described two patients with late syphilis, one with asymptomatic neurosyphilis, the other with an aortic aneurysm, both with positive serologic tests, who following adequate treatment with arsenicals and bismuth and resulting seronegativity were seen about three years later with newly acquired syphilis[113]. Another case is that reported by Gibbons and Walsh of a colored man with aortic insufficiency, a history of a penile sore 15 years earlier and a positive Wassermann reaction, who developed a dark field positive penile lesion 4 days after venereal exposure[114]. Schoch and Alexander comment on the frequency of reinfection in syphilis when adequate treatment is given early and describe 10 such cases, in two of which serologic tests were still positive in low titer at the time of reinfection. One patient apparently was infected with syphilis three times during one year[115].

Patients with known syphilis have been inoculated with yaws spirochetes in an attempt to measure immunity. Jahnel and Lange, who inoculated 9 neurosyphilitics with strains of *T. pertenue* obtained from infected rabbits, failed to produce lesions in all but one, in which a granuloma containing spirochetes developed[116, 117]. Van der Schaar inoculated 26 general paralytics with yaws material with positive results in only one case. However, the original diagnosis in this case may have been incorrect since both spinal fluid and serologic tests were normal[118]. The preponderance of negative results was interpreted as evidence of the close similarity of the two diseases and of the development of a

tion may have changed with successive human transfers under suitable environmental conditions so that a florid yaws type of response is the result In this connection it is possible that one strain of organisms may pass through at least 3 or 4 human transfers each year or as many as 150 to 200 transfers in 50 years sufficient perhaps to produce modifications of the clinical pattern of response However immunity probably is the important factor in suppressing syphilis in a yaws population

On the other hand although florid yaws cases have been repeatedly introduced into areas such as the Virgin Islands and the United States where syphilis is prevalent yaws has not become endemic The factor of resistance to yaws as a result of previous infection with syphilis probably has had little or no effect in the failure of yaws to persist In the first place even in areas where syphilis attains its greatest prevalence the majority of the population especially the children are not infected and therefore are non immune Most of the potential contacts of a case of yaws would be susceptible and the failure of yaws to persist must be explained on some basis other than immunity The most reasonable explanation is that environmental conditions do not favor the transmission and development of yaws It is to be remembered that the clinical pattern of yaws may be modified by climate with a less profuse drier and therefore less contagious type of eruption in the colder, drier environment of the United States or in the drier and more barren area represented by the Virgin Islands This would hinder contagion and at the same time favor the evolution of a new pattern of disease

There have been numerous clinical observations reported which are interpreted variously as evidence for or against a cross-immunity between yaws and syphilis Rat in his classical monograph on yaws, as a differential point between it and syphilis says that yaws or syphilis may be contracted by persons suffering from the other condition[111] McKenzie reported what he believed to be a case of syphilis in a 20-year old Polynesian boy who had yaws The patient was first seen with a typical framboesial eruption on the face and chest He was given 3 injections of neoarsphenamine at weekly intervals with disappearance of all lesions When seen a year later he presented what was said to be a typical mucous syphilid on the lip a typical yaw at the right nostril and another between the nates as well as a Hunterian chancre on the prepuce the latter having appeared about 2 weeks after intercourse with a known prostitute[112] It is possible that yaws had persisted in this patient but that the immunity which developed was not solid enough to prevent symptomatic superinfection with a new strain of treponemata

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The incubation period of yaws the time interval between effective exposure and the first noticeable lesion is generally stated to average from 3 to 6 weeks but it may be as short as two weeks or longer than three months Under natural conditions it is difficult to measure the incubation period exactly because the presence of many potential sources of infection makes it impossible to determine when effective exposure occurs However inoculation experiments of Paulet[34] Sellards and

reciprocal immunity. Turner failed to produce lesions in 10 patients with seropositive latent syphilis inoculated with *T. pertenue*. He concluded that syphilis confers an immunity to yaws which may be greater than that conferred by yaws itself[illegible]

Records of experimental infection of animals provide further evidence concerning immunity in yaws and syphilis which, with some exceptions, is in general agreement with the experience in humans. On the basis of a few observations in rabbits Nichols thought that there was some cross immunity between the two types of infection which varied somewhat with different strains of spirochetes[17]. Schobl and Miyao[illegible] inoculated with syphilis monkeys which had been infected with yaws for more than 12 months and which were resistant to reinfection with *T. pertenue*. The fact that either no lesions or only small abortive papules developed at the site of the new inoculations was interpreted as evidence of resistance to syphilis. Matsumoto[31] stated that local lesions were quite regularly produced by yaws material inoculated into rabbits infected with syphilis for periods of several months to more than two years, and also that rabbits rendered immune to symptomatic superinfection with yaws spirochetes regularly developed obvious syphilis lesions after inoculation with *T. pallidum*. These studies were thought to indicate the lack of development of any great degree of cross immunity. In contrast, Turner and others found that as early as six months after infection with either *T. pertenue* or *T. pallidum* rabbits showed an appreciable degree of immunity to both types of spirochetes, even when the challenge inoculations contained probably thousands of times the minimal infective dose of these organisms for rabbits. They felt that their results were consistent with other experimental, clinical and epidemiologic evidence of serviceable degree of cross immunity between yaws and syphilis, and that it was unlikely that the introduction into man of such enormous numbers of spirochetes would ever occur under natural circumstances[19].

It seems clearly established that infection with yaws results in the development in the host of a resistance not only against the treponemata which are living in that host with a resulting evolutionary clinical pattern tending toward latency and biologic cure but also against heterologous strains of treponemata including *T. pallidum*. Resistance develops slowly during the first few months or years of infection, it is relatively weak and may be overcome provided the reinfecting dose of organisms is large, but later, a more solid immunity is built up and either an atypical abortive response by the tissues of the host will result

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associates[103] and others indicate that the primary lesions appear about three or four weeks after inoculation. It has been shown that, at times, only a small, abortive papule develops at the inoculation site, a lesion which might be easily overlooked, but it is probable that in the great majority of instances infection results in an obvious granulomatous initial lesion. The time required for the development of a recognizable primary lesion may be influenced by various factors such as the number of spirochetes introduced, the site of inoculation and by the environment. The introduction of a few treponemes probably results in a longer incubation period than the introduction of many. It is not possible to know the number of spirochetes which are transferred during contact with an infectious yaws lesion or in other ways. It is probable that, if a given quantity of organisms is available, the number actually gaining entrance into the host will depend somewhat upon the avenues which are open for invasion. Thus a pre-existing ulcer would provide opportunity for invasion by a larger number of treponemes and a shorter incubation period than a small cut or abrasion which would admit relatively few organisms, the remainder dying on the surface of the skin. Under the latter conditions the incubation period would be longer. By analogy with syphilis it is likely that yaws spirochetes do not penetrate the unbroken skin, although they may invade intact mucosae. That the site of invasion may affect the incubation period is suggested by the fact that in rabbits the skin of the scrotum provides a more suitable location for the initial multiplication of *T. pertenue* than the skin of the back.[9] Furthermore, in rabbits a larger number of *T. pallidum* are required to produce infection when inoculated into the skin of the back than when inoculated into the testis.[10] That environmental factors of temperature and moisture somehow influence the course and development of yaws in humans has been emphasized already, and it is felt that the incubation period may be prolonged when infection occurs during a spell of cool, dry weather. In this connection it is well known that both yaws and syphilis in rabbits have a longer incubation period and show fewer obvious lesions in a hot than in a cold environment.[51, 9] Apparently the influence of temperature on the course of these infections in rabbits is just opposite from the effect upon human yaws, but there is no ready explanation for this seeming inconsistency.

It is said by some that malaise, rheumatic pains and fever occur during the incubation period of yaws,[1, 11] but this was not confirmed by the experience in Jamaica. Symptoms occurring during the incuba-

tion period of yaws are more likely the result of some intercurrent condition such as malaria, influenza or other infection

Primary Lesion

The initial lesion of yaws usually is readily recognized as the first stage of the disease by the afflicted native peoples who call it by various names such as the mother yaw in English, the madre buba in Spanish or the mamma pian in French In most instances a recognizable primary yaw develops at the site of inoculation but in some the lesion may either fail to appear or be so slight as to pass unnoticed However nearly all yaws patients can recall the mother yaw and frequently display a residual scar at the site

The primary lesion is located most often on the lower extremities but it may occur on any part of the body The frequency of location of the primary lesion on the lower extremities or elsewhere apparently varies somewhat depending on the age at the time of infection on sex on the habits and customs of the population and on the general prevalence of the disease Probably the most important factor in determining location of the initial lesion is trauma with resulting breaks in the integument Another factor is doubtless the frequent presence of non specific ulcers about the lower legs and ankles and this localization too is in part determined by injuries Moss and Bigelow[121] determined the location of the primary yaw in nearly 1 000 cases in the Dominican Republic from either the medical history with or without a confirmatory scar or from actual observation of the lesion They found that the first lesion occured on the lower extremities in about 83 per cent of cases on the upper extremities in about 8 per cent and on the genitalia in only about 1 per cent Primary lesions on the lower leg occurred most often on the anterior surface and least often on the posterior surface When they developed about the ankles they were located over the internal or external malleolus in the great majority of cases It was concluded that in a bare-footed bare legged population the lower extremities would be the most frequently traumatized part of the body and that this was an important factor in the localization of the primary yaw Essentially similar observations were made in Jamaica[60] where the initial lesions were observed in more than 300 cases and the location determined in more than 1 000 others from the history In this group the primary

sore occurred on the lower leg in 77 per cent of cases, on the hand or arm in about 9 per cent about the head or neck in about 8 per cent, on the breasts or other trunk areas in 6 per cent and on the genitalia in less than 3 per cent Practically all cases where the genitalia were first involved were in pre adolescent children Just how frequently venereal contact was responsible for the l ... lization of the primary lesion is unknown, but since syphilis is not infrequently acquired in childhood and early adolescence by sexual contact it is probable that yaws likewise may be transmitted in the same way In older age groups particularly in females between the age of puberty and the fifth decade the primary lesion was located ... frequently on the upper extremities the head neck or the trunk ... younger groups This is probably accounted for by the fact that ... are exposed more to yaws because they care for younger children among whom the disease is most common holding them in their arms or nursing them at the breast In this connection Findlay noted that in West Africa where primary yaws was commonest between the ages of ... to ... years there appeared to be a rise in incidence among women in the early twenties He cited 8 young women with primary lesions on the breast or chest the infection having been caught from yaws infected children who were breast-fed According to Findlay s observations the distribution of primary lesions is quite different in West Africa from most other yaws areas In 100 consecutive cases of primary yaws seen in the Gold Coast the lesion was located about the buttocks perineum or thighs in 57 about the face in 16 and on the lower legs and ankles in only 11 He thought that the parts of the body in contact with the ground when the person is sitting are the areas most commonly affected This is in marked contrast to Jamaica where among 80 cases of primary yaws observed in children less than 5 years of age the lesion appeared on the leg in 63 per cent The reasons for such differences are not apparent

Where environmental factors tend to suppress the eruptive lesions and to localize them more about the mouth or perineum it is likely that the initial lesion itself likewise will be located more often about the mouth or genitalia and consequently adult infection will occur more frequently Such influencing factors were doubtless present in the mountain area of the Philippines already referred to[89] where frequent involvement of the genitalia indicated that the disease was actually contracted by sexual contact in some cases Unfortunately the locations of the first yaws lesions among this group was not stated

Typically the initial yaws (Fig 1) papule gradually enlarges becomes raised above the surrounding skin and the surface epithelium ulcerates with the production of a serous discharge which on drying forms a grayish yellow crust When the crust is removed, the surface of the papule is seen to be coarsely granular the reddish granulations providing the supposed similarity to a raspberry In size the full blown primary lesion may vary from one centimeter or less to several centimeters in diameter and is elevated several millimeters above the surrounding skin surface Several weeks are required usually for the development of the initial lesion to this stage This mother yaw may persist for several



Fig 1 Primary lesion on lower leg Note central crusted area and surrounding areola

months particularly if the infection is implanted on a pre existing ulcer or it may heal in the course of a few weeks Healing commonly leaves residual scarring characterized by increased pigmentation and thin atrophic parchment like epithelium

The character of the primary yaw is doubtless modified somewhat by its location and by the presence of an ulcer at the site of infection On the lower legs and feet secondary infection and trauma favor the development of the process and larger more persistent lesions are the

result If a non specific ulceration is already present this feature may be so accentuated that the granulomatous character of parts of the lesion may be overlooked As a rule when the initial lesion develops on the head the neck the trunk or the upper extremities it is similar in all respects to the typical secondary granulomata which ordinarily appear later and consists of a raised crusted sharply circumscribed granulomatous papule with but little induration about the base



Fig 2 Primary lesion on neck Satellite buboes are obvious Material aspirated from buboes revealed *T pertenue*



Fig 3 Primary lesion on foot Surrounding areola is well shown Photograph shown in Fig 3 provided by Dr Cid Ferreira Lopez of Brasil

Frequently there is a halo or areola of scaling skin around the initial papule, several centimeters wide and at times smaller satellite papules may be seen developing in this area This particular feature has been emphasized by Ferreira Lopez[121] who observed it frequently in yaws cases in Brazil The areola perhaps results in part from bacterial infection but more likely it represents direct radial spread of *T pertenue*

through the lymphatics The lymph nodes draining the primary site usually are enlarged and firm, and material aspirated from them commonly reveals *T pertenue* which are found also in great numbers by dark field examination of serum from the surface of the primary lesion Figs 1, 2 and 3 illustrate primary yaws lesions

Serologic tests begin to become positive during the second or third week after the appearance of the primary papule, and quantitative techniques have demonstrated a rising titer over a period of weeks High titers may be attained and may persist for many years in the absence of specific treatment[30] General constitutional signs or symptoms usually are absent during the early days of primary yaws However since bone pains and slight fever may accompany early generalization of the infection, these symptoms may be a prominent feature while the primary lesion is still present and before obvious secondary lesions appear

Generalization of the Infection

In most if not all cases of yaws the first spread of *T pertenue* from the portal of entry is by way of the lymphatics Invasion of the blood stream probably occurs within the first few days of infection and results in manifest lesions in widely separated parts of the body Obvious lesions are common in the skin subcutaneous tissues bones joints and tendon sheaths and it is likely that other tissues are invaded although clinically demonstrable changes may not be produced At times it is difficult, if not impossible to differentiate changes belonging to the secondary stage of yaws from those of the so-called late stage Gummatous nodules or ulcerations may appear early while the florid granulomatous lesions are still present and granulomatous dark-field positive lesions may reappear years after the primary and generalized skin eruptions have healed and at a time when gummatous lesions are present also Therefore for the sake of clarity the manifestations of early and of late yaws will be described without undue stress on the chronological order of their appearance

Secondary Skin Lesions

Generalized skin lesions commonly make their appearance within a few weeks after the initial lesion, but they may not develop for several

months and in rare instances the early lesions of the disease may be so slight and so evanescent as to pass unnoticed In this connection, in a population group studied in rural Jamaica where yaws was prevalent and syphilis rare a significant number of persons were found who denied early lesions of yaws but whose serologic tests were positive and in some late ulcerative and other types of lesions were found probably due to yaws



Figs 4 and 5 Generalized framboesiform yaws

The skin eruption of early generalized yaws commonly is polymorphous and subject to great variation and the classical picture of a profuse framboesiform rash is observed in only a minority of patients Lesions may be predominantly macular or papular, but annular and circinate eruptions are common also Hackett has stated that of all yaws lesions that most commonly recognized as yaws is the scattered eruption of raised, granulomatous papules[1 5] Rat in his description of the evolution of a typical case said that the patient is covered from head to foot with

minute red spots some of which develop into conical papules but the majority of which disappear The persisting lesions become larger and crusted and they measure on the average about a quarter of an inch in diameter and an eighth of an inch in height and under the crusts is a mass of granulation tissue covered with a creamy secretion [111]

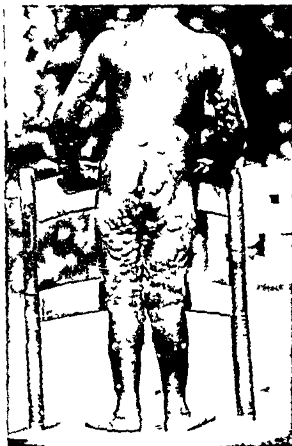


Fig 6 Generalized framboesiform yaws

Cases of typical generalized framboesiform yaws are shown in Figs 4 5 and 6 For comparison two photographs of cases of early syphilis seen in the United States are included (Figs 7 and 8) These represent types of syphilitic lesions which are not uncommon in negroes Fig 8 representing a framboesiform secondary syphilide It is apparent that

at least at the stages of evolution represented by the illustrations on a purely morphological basis it may not be possible to distinguish between the two patterns of infection

A desquamating macular type of secondary rash may develop either as a single type of lesion or together with scattered papules This type of eruption sometimes is called the yaws spots or yaws trash" by



Fig 7 Annular secondary syphilis Photograph provided by Dr Harry M Robinson



Fig 8 Framboesiform secondary syphilis Photograph provided by Dr Harry M Robinson

Jamaicans There may be widespread scaling macular areas varying in size from a few millimeters to several centimeters At times the periphery of the spots may show branny desquamation with little obvious change in the center of the lesions or there may be central atrophy and scarring Fig 9 illustrates the macular type of rash

A tendency to hyperkeratosis is often noted and folliculo papular

lesions are not uncommon Occasionally groups of pin point projections of the corium may give the impression of a nut meg grater Fig 10 shows the folliculo papular type of yaws lesion These lesions are similar to those described in syphilis as the papulo squamous type of syphilide, illustrated by Fig 11



Fig 9 Scaling macular yaws eruption

Condylomatous lesions frequently are found about the perineum (Figs 1 and 13) and grossly cannot be distinguished from the condylomatalata of syphilis (Fig 14) Not uncommonly secondary yaws lesions may assume an annular configuration as shown in Fig 15

Although cases may be seen in which the lesions remain predominantly macular or follicular and subside within a few weeks or months without the development of crusted framboesiform papules, characteristically a few or several such papules will appear. Other cases are seen which first show myriads of small papules, many of which later develop into typical framboesiomata. The course and evolution of the secondary eruption probably are affected by many factors, some inherent in the host and a result of the immune response, while others are



Fig 10 Folliculo papular yaws



Fig 11 Secondary syphilis papulo squamous type Photograph provided by Dr Harry M Robinson

environmental. Rat[111] in commenting on the effect of external temperature on the evolution of yaws stated that undue exposure to cold may suppress the eruption partially or entirely. In the majority of cases the secondary eruption, regardless of type, gradually subsides and disappears within a period of several weeks or months, but in some cases a granulomatous eruption may continue for years, new lesions appearing from time to time until immune processes finally suppress the infection.

and the disease either becomes latent or it is overcome entirely Residual scarring which may last for many years frequently follows the more extensive and florid types of eruption The scars are circular or oval and although they commonly show increased pigmentation occasionally there may be a loss of pigment At times there is atrophy of skin in the



Figs 12 and 13 Condylomatous yaws

scarred areas which appear crinkled and are covered with thin epithelium *T pertenue* usually can be demonstrated with ease in the serum from crusted papules and also in that obtained by scraping the non ulcerated lesion such as the follicular and macular types As a rule there

is generalized enlargement of lymph nodes in keeping with the distribution of the skin lesions and fluid obtained from such nodes likewise shows the presence of *T pertenue* The various serologic tests for syphilis are invariably strongly positive during the stage of early generalization

Lesions of Mucous Membranes

Not infrequently papular yaws lesions develop on the lips around the anus or on the eyelids but in Jamaica at least secondary lesions



Fig 14 Condylomata lata of syphilis Photograph supplied by Dr Harry M Robinson



Fig 15 Annular type of secondary yaws lesion

invading the mucosae of the pharynx were not seen On the other hand Castellani and Chalmers[16] who stated that such lesions were not common in yaws described small granulomatous nodules at the base of the tongue and on the nasal mucosae and whitish patches closely resembling syphilitic leukoplakia in the mouth during the secondary stage Noel[17]

reported that he found secondary lesions on the mucosae of the mouth in 2- of 100 cases of generalized yaws seen in the Cameroons Hackett[19] stated that in cases of florid yaws in Uganda about per cent showed small lesions somewhat resembling modified skin lesions on the faucial pillars uvula hard palate and tongue Numerous spirochetes indistinguishable from *T pertenue* were seen in scrapings from these lesions and a biopsy specimen from one case showed changes similar to early yaws skin lesions and spirochetes of the yaws syphilis type Undoubt



Fig 16 Plantar papular yaws



Fig 1 Plantar papular yaws with obvious macular lesions

edly mucous membrane lesions occur during the secondary eruption of yaws but apparently the frequency with which they are found varies from place to place It may be that such variations are further evidence of modification of the clinical pattern by external influences It is well known that mucous patches are a common manifestation of secondary syphilis and Hudson[6] commented both upon the frequency of mucous

membrane lesions in the childhood syphilis of the Arabs and upon the relative feebleness of the secondary skin eruption

Palmar and Plantar Lesions

Lesions of the palms and soles (Figs 15 to 20) are frequent during the period of the secondary skin manifestations and may persist or recur for many years The lesions are of two general types One is a granulomatous papule which erupts through the overlying epidermis to form a conical protuberance above a circular ulcerated base This type of

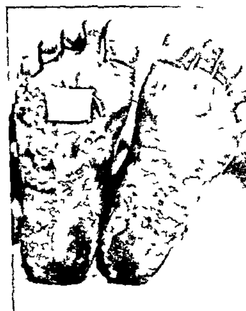


Fig 18 Hyperkeratotic and scaling plantar yaws



Fig 19 Hyperkeratotic plantar yaws

lesion is particularly common on the plantar surfaces and may be bilateral with one or several papules on each foot Plantar papules are painful as well as disabling causing the patients to shuffle along bearing their weight on the sides of the feet Because of the peculiar gait a common name for the condition is "crab yaws" Trauma and secondary infection retard healing of such lesions which may persist for many months Plantar papules are the commonest type of infectious relapsing lesion and they may recur every year or two for as long as 15 to 20 years There is a noticeable seasonal occurrence in this type of relapsing lesion which

develops most often during periods of heavy rainfall In Jamaica it was a common experience to hear the patients state that the crab yaws break out every year during the rainy season At this time the skin of the feet of the barefooted country Jamaican frequently is wet and muddy for hours at a time while walking on the trails or fields or at work on the plantations and in consequence the skin becomes soft and more susceptible to injuries which may predispose to the development of yaws papules

In Jamaica among nearly 1 700 cases of yaws with some type of active lesions crab yaws was the only observed lesion in [illegible]0 cases or about 13 per cent and accounted for more than 40 per cent of all infectious types of lesions Since these granulomatous plantar lesions were observed more frequently among males than among females trauma is again implicated as a predisposing cause since males suffer greater trauma of the feet than females because of their greater physical activity Papular lesions of the palms occur less frequently and are less apt to relapse after long periods Trauma also appears to play a part in localizing palmar lesions which often develop only on one hand that which holds the machete or other tool of the workman

The other type of plantar and palmar lesions is characterized by a marked hyperkeratosis with great thickening of the palms and soles (Figs 18 and 19) This may be a diffuse generalized process affecting the entire surface or it may occur in a patchy macular pattern with less thickening and with normal appearing intervening skin The surface of the skin is roughened often pitted giving a moth eaten appearance scaling is common and deep painful fissures may develop This type of keratotic lesion occurs as a rule later in the course of the disease than the papular type and may persist for many years with little change except scaling and occasional fissuring It is a common type of lesion of the soles but it is seen much less frequently on the palms Open plantar or palmar papules may be present also and some hyperkeratosis is nearly always found in association with papular lesions of the palms and soles

Granulomatous plantar lesions of yaws are illustrated by Figs 16 and 17 the latter showing macular patches of hyperkeratosis Numerous *Hippelates* flies may be seen feeding on the open lesions The hyperkeratotic and scaling type of plantar lesion is illustrated in Figs 18 and 19 Scaling palmar lesions with one open papular lesion are shown in Fig [illegible]0

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In Jamaica among nearly 1 700 cases of yaws with some type of active lesions crab yaws was the only observed lesion in 220 cases or about 13 per cent and accounted for more than 40 per cent of all infectious types of lesions Since these granulomatous plantar lesions were observed more frequently among males than among females trauma is again implicated as a predisposing cause since males suffer greater trauma of the feet than females because of their greater physical activity Papular lesions of the palms occur less frequently and are less apt to relapse after long periods Trauma also appears to play a part in localizing palmar lesions which often develop only on one hand that which holds the machete or other tool of the workman

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to the hyperkeratotic lesions of Arab tribal syphilis described by Hudson[8] and it would be difficult if not impossible, to distinguish between the two conditions on the basis of plantar lesions alone Furthermore, clinical urban syphilis frequently produces similar plantar and palmar lesions as illustrated in Figs 1 and 2



Fig 20 Palmar yaws Hyperkeratosis and scaling one open papule



Fig 21 Plantar lesions of syphilis Photograph supplied by Dr Harry M Robinson

Lesions of Bones and Joints

The skeletal system is involved frequently in yaws both early and late in the course of the disease (Figs 23 to 31) Hermans[1] who summarized the reports of many observers indicated that bone and joint lesions had been attributed to framboesia for at least a hundred years but in spite of the frequency with which skeletal yaws has been described during the past century the concept of yaws is only a skin infection persisted and in the face of overwhelming evidence to the contrary some

observers have maintained that *T pertenue* does not invade the bones However the frequency with which bone lesions are found in yaws patients lesions causing painful tender swellings associated with structural changes demonstrable by x rays the favorable response of many



Fig Palmar lesions of syphilis Photograph supplied by Dr Harry M Robinson

such lesions to specific therapy and the production of bone lesions in experimental yaws in rabbits[1] leave no doubt as to the etiologic role of yaws in the production of bony abnormalities

The stated frequency with which yaws affects the skeletal system either early or late in the course of the disease has varied widely among

different observers probably depending somewhat upon the care used in searching for such lesions Rat[111] in his classic monograph on the disease described inflammation of the periosteum of the cranium the clavicle the sternum and ribs the ulna the tibiae and the metatarsals during the secondary stage During what he called the tertiary period he noted diffuse chronic periostitis often associated with ulceration of



Figs 23 and 24 Bone lesion in yaws

overlying tissues, dactylitis and joint swelling Maul[130] indicated that about -0 per cent of yaws patients in the Philippines showed bone lesions Moss and Bigelow[121] stated that dactylitis and arthritis most frequently involving the knees and elbows, were fairly common early

in the disease In the tertiary stage they saw patients with periosteal thickening of the long bones particularly of the tibia radius and ulna some with spindle shaped swelling of the fingers and others with destructive lesions of the cranial bones the nose and hard palate The authors were unable to decide whether the tertiary bone lesions were due to syphilis or yaws Hunt and Johnson[121] who studied 2 000 cases of yaws in American Samoa stated that painful swollen joints were a frequent finding and that nearly 20 per cent showed involvement of the bones during the secondary stage Chronic periostitis was common during late stages of the disease In Jamaica most patients complained of pains in the bones and joints sometimes as early as three to five weeks after the appearance of the primary lesion[4] and it was thought that lesions occurred in the great majority of patients during the first few months or years of the disease There was definite x ray and other objective evidence of involvement in about 25 per cent of cases of yaws[67 94] Hackett[123] found that joint involvement of the knees with hydrarthrosis was common and that evidence of multiple bone lesions was seen in the majority of cases of early yaws in Uganda

There are certain differences in the extent character and time of appearance of osseous involvement which suggest a broad classification into two groups (a) those occurring early in the disease usually within the first few years and not infrequently associated with some form of secondary skin lesions and (b) those occurring from a few to many years after the onset of the disease and frequently associated with late destructive and ulcerative lesions of the skin

It is the rule that bone pains occur during the first few months of the yaws infection The pains may be referred to almost any part of the body, but usually the legs arms knees or elbows and the skull are involved Examination may reveal objective evidence of bone and joint lesions The joints may be swollen tender and hot with signs of increased fluid There may be numerous tender swellings along the course of the long bones particularly of the legs and arms but any bone may be involved These early lesions frequently are widespread in many different parts of the body with multiple lesions in the affected bones Ulceration of the overlying skin is not a common finding in this early type of lesion although non specific leg ulcers may be associated with extensive involvement of underlying bone the tibia for example with thickening and sclerosis of the cortex and the formation of bony spurs Roentgenograms reveal evidence of structural changes in the majority of patients with signs or symptoms of bone lesions The x ray appearance may be

that of scattered multiple areas of cortical rarefaction in either the diaphysis or epiphysis of long bones (Fig. 25) or in the substance of the flat bones. There may be evidence of increased density in the bone surrounding the rarefied areas. Frequently periostitis is found with elevation of the periosteum and the formation of new bone (Fig. 26). Both rarefaction and periostitis may be seen in the same bones, or they may occur independently. Another type of bone lesion results in a general increase



Fig. 25. Early bone yaws: multiple rarefied areas

Fig. 26. Yaws periostitis with thickening of cortex

in the circumference and in the density of the shaft of long bones. This is an osteitis which is found usually in cases in which bone changes have persisted for many months even though signs and symptoms of acute involvement have long since disappeared. It is this chronic type of lesion, difficult to classify as early or late, which may result in the severe de-

formities such as are represented by 'sabre shins' or by 'boomerang legs'. In most cases in which acute joint involvement occurs x rays show evidence of involvement of one of the adjacent epiphyses with single or multiple areas of rarefaction which extend outward to the joint cartilage. Spindle shaped swellings of the fingers on x ray examination commonly show fusiform swelling of the phalanges with or without



Fig 27 Yaws dactylitis

punched out destructive lesions of the cortex (Fig 28). Dactylitis may occur early or late in the disease and it is not possible to assign this lesion to either of the two general types of bone yaws. The x rays shown in Figs 23 and 24 are those of a 6 year old girl with yaws of years dura

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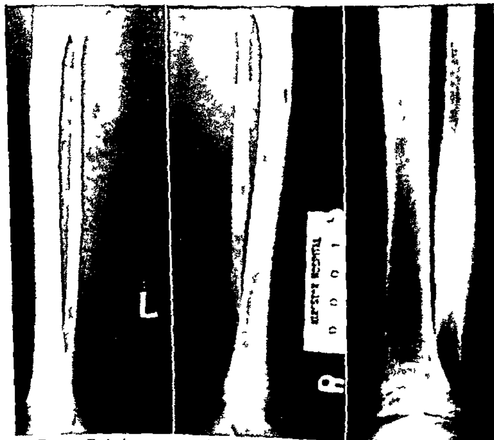


Fig 25 Early bone yaws multiple rarefied areas

Fig 26 Yaws periostitis with thickening of cortex

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tion. Multiple areas of rarefaction are seen in each fibula. Another example of a similar lesion is shown in Fig. 25, which illustrates multiple areas of rarefaction with surrounding increased density in the tibia and fibula of a 9 year old girl who had yaws for about a year. Fig. 26, the x-ray of an 8 year old girl with early yaws, shows a lesion in the lower third of the fibula, a periostitis with considerable thickening of the un-

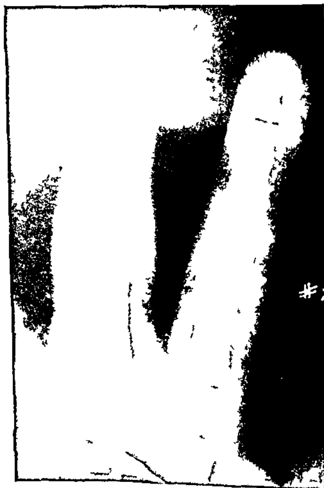


Fig. 28. Yaws dactylitis

derlying cortex. Fig. 27 is a photograph of a fusiform swelling of the middle finger of a boy 10 years old who had yaws about 5 years previously, and Fig. 28 shows the x-ray appearance with involvement of the

cortex and periosteum of the distal third of the proximal phalanx and an area of rarefaction in the proximal end

The early type of bone yaws responds promptly to specific therapy Pain and tenderness disappear quickly swelling gradually diminishes and x ray findings tend to become normal within a period of several weeks or months

Late bone yaws lesions usually are not so widespread as early lesions, fewer bones are involved as a rule and there are fewer lesions in the individual bones Late lesions are more chronic in their course with



Fig 29 Destructive type of late bone yaws



Fig 30 Late bone yaws

fewer and less severe symptoms However considerable enlargement of bones may result in severe deformities and associated ulcerative skin lesions are found frequently which may be directly continuous with diseased bone As in early lesions late bone lesions may involve any part of the body but the commonest sites are the long bones of the legs and arms the clavicles and the cranium The characteristic radiographic

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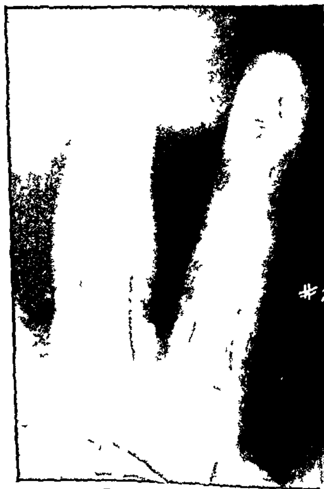


Fig 28 Yaws dactylitis

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frequently than in areas where the majority of cases receive some treatment early in the disease

Gondou commonly develops early in the course of the disease and should be classified with the secondary manifestations although the hard bony protruberances may persist permanently if treatment is not given promptly The onset of gondou frequently is marked by persistent



Fig 31 General thickening of cortex in late bone yaws

headache worse at night and there may be a purulent or bloody nasal discharge The involved bones gradually enlarge forming hard oval masses which usually but not always are bilateral As the exostoses grow larger they may form masses several centimeters high which inter

appearance of late bone lesions may be that of well defined cortical rarefactions usually localized Marked enlargement of the involved bone may result There may be considerable evidence of new bone formation with sclerosis and thickening of the shaft adjacent to the cortical rarefactions These lesions may extend outward and ulcerate through the skin with the formation of nodular or nodulo ulcerative gummata At times fusiform enlargement of the shaft due to thickening of the cortex is the predominant feature

Fig 29 illustrates a destructive type of late bone lesion with bulging of the cortex over a rarefied area in the left humerus of a woman 22 years old who had had yaws since about 7 years of age Fig 30, a photograph of the same patient shows swelling of the left wrist, and Fig 31 is the roentgenogram demonstrating changes in the left radius characterized chiefly by new bone formation although some areas of destruction may be seen also

Specific therapy usually will stop the progress of late bone lesions Overlying ulcerations heal promptly and areas of rarefaction disappear, but there is commonly little change in the proliferative bone involvement, and the deformities resulting from such lesions may be permanent

Gondou — This striking condition results from bony overgrowth of the nasal bones and the nasal processes of the maxillae which causes swelling at the sides of the nose (Fig 32) Hermans[1] stated "In 1882 MacAlister drew attention to this remarkable condition in his publication entitled 'Horned Men in Africa' Patients suffering from gondou have a swelling on both sides of the nose growing on the bone and leaving the skin intact forming first round bumps and then spreading over the bridge of the nose, and the cheeks —"

Gondou has been the subject of much discussion since it was first described and many theories as to its etiology have been advanced but it is now generally accepted that it results from yaws[3] It has been reported from nearly all tropical areas where yaws prevails but apparently it is of rare occurrence in some regions and common in others Only a few cases were seen in Jamaica during the examination of many thousands of yaws patients but apparently gondou occurs with great frequency in yaws in Africa Hackett[12a] reported that he saw minor degrees of gondou in 23 patients or 15 per cent of 152 cases of secondary yaws with associated bone involvement It is probable that differences in incidence of gondou reflect the differences in the availability of treatment for yaws In areas where yaws is untreated gondou is seen more

to decrease in size or to disappear altogether but in long standing cases with large swellings there is little response to therapy, and surgical removal of the bony masses may be necessary where vision is obstructed Fig 32 illustrates a case of a minor degree of gondou



Fig 33 Gangosa

Gangosa Rhino pharyngitis Mutilans

Gangosa (Fig 33) is a term which according to Butler[132] has been in use for several hundred years to describe the mutilating deformity which results from the destruction of the soft and bony structures of the face with consequent interference with speech, hence, gangosa', which

fere with vision They may encroach on the nasal passages causing obstruction but according to Strong[3] they do not tend to invade the orbits Findlay[14] describes the development of gondou in a West African The patient, a 12 year old boy, developed yaws, and 3 months



Fig 3 Gondou Photograph provided by courtesy of Dr C J Hackett and reproduced with permission of the Editor Transactions Royal Society of Tropical Medicine and Hygiene

later was given three injections of a bismuth preparation Six months afterward he developed bilateral gondou periostitis of the right tibia and involvement of the left internal malleolus with an overlying ulcer

Adequate specific treatment if given early enough will prevent gondou or will stop its further development and cause the swellings either

time the etiology of juxta articular nodules was the subject of much dispute there is now general agreement that yaws or syphilis is the cause in most instances but that similar nodules may occur in cases of onchocerciasis[133 131] in rheumatoid arthritis and possibly in some other conditions The apparent relative scarcity of the condition in temperate climate



Fig 34 Juxta articular nodules

where syphilis is common may be due to the fact that the nodules have been incorrectly attributed to some other cause[135] or because treatment which is more available outside the tropics has prevented their development[133] While only about 200 cases have been reported from non tropical regions and only 30 of those from North America[135] it has been

means muffled voice The condition is now recognized as existing in those parts of the world where yaws is prevalent It occurs with relative frequency in localities where proper treatment is not available or among ignorant unhygienic people who neglect treatment , but it is seldom seen where adequate treatment is given In Jamaica, where a relatively large proportion of cases of yaws receive some treatment, destructive ulcerative lesions of the bones and soft tissues of the face are uncommon and among more than 7 000 yaws cases examined in clinics there were only 14 or about two per thousand who had such lesions, most of them being of minor importance

Gangosa should be classified as a late yaws lesion, because it seldom appears until several years after the onset of the disease and long after secondary skin lesions have disappeared There may be associated ulcerative lesions of the skin and bones of other parts of the body The process begins either as a small ulcerated nodule on the mucosae of the nasal septum or palate secondarily involving the bone or as a gummatous lesion in the bones which ulcerates through the mucosae The ulceration may continue to spread involving adjacent structures until the nasal septum the hard palate, the nasal bones and the covering soft tissues are completely destroyed leaving an open cavity replacing the central part of the face The progress of the lesion may be halted at any time by the immune processes of the host or by specific treatment Cases are seen with only perforation of the palate or of the nasal septum, either in the bony or cartilagenous portion or both but in the absence of treatment the process usually goes on to more extensive destruction Gangosa differs from other destructive, gummatous lesions of bones and soft tissues only in its location in the central facial structures where mutilating deformities are liable to be more disabling and more hideous than lesions of equal size elsewhere on the body Fig 33 shows a case of gangosa

Juxta articular Nodules

Juxta articular nodules (Figs 34 35 and 36) are painless discrete fibrous nodules situated in the subcutaneous tissues in the region of a joint or a bony prominence They are usually of slow growth are freely movable and are not attached to adjacent skin, bursae or tendon sheaths In general their geographic distribution in the world coincides with that of yaws or with primitive syphilis and they are encountered most often in the tropics where these conditions are common[133] Although for a long

or about 8 per thousand patients There was considerable difference in the frequency of the condition according to sex females being affected about three times as often as males (1 4 as against 4 8 per thousand)

Juxta articular nodules seldom occur in children or young adults In the group of 110 cases studied in Jamaica none of the patients was less than 5 years old only 3 were less than 10 years old and the majority were more than 40 years of age Infection with yaws had occurred as a rule many years before the nodules first appeared although in a few cases the duration of the infection was less than 5 years Nodules developed as early as years and as late as 60 years after infection the average being about 25 years therefore they should be considered as late lesions from the standpoint of time of development in the course of yaws In about two thirds of cases with juxta articular nodules no other lesions of yaws were found In the remaining patients some other type of lesions occurred commonly hyperkeratosis and scaling lesions of the plantar and palmar surfaces occasionally late lesions of the skin or bones and rarely infectious lesions such as open plantar papules

Nodules were found mainly in patients who had been given no treatment or at most only one or two injections of bismuth early in the course of the disease Thus they were more prevalent among patients from those districts furthest removed from treatment centers

The favorite site for these nodules appears to be the tissues over the extensor surfaces of the elbow and knee joints Less frequently they are seen over the malleoli the greater trochanters the temporomandibular shoulder sternoclavicular or finger joints and only occasionally elsewhere In some cases single nodules are found but in many they are multiple and occur in the region of several different joints or bony prominences They may vary from barely palpable nodules a few millimeters in size to large masses many centimeters in diameter Serologic tests commonly are positive In the Jamaican series the Wassermann reaction was positive in 94 per cent of 103 cases tested Figs 34 35 and 36 illustrate typical nodules seen among yaws patients in Jamaica

The response of juxta articular nodules to specific therapy is definite but slow and appears to be less marked in patients who have had nodules for many years In the group seen in Jamaica following treatment with bismuth or arsenical preparations the nodules gradually became smaller softer and in a period of several months to a year many of them had disappeared altogether In other cases there was little or no obvious response although the amount of therapy may not have been adequate

estimated that in some tropical areas 1 or 2 per cent of the population may be affected[131]

The frequency of occurrence and the clinical manifestations of juxta articular nodules was studied in Jamaica[138] Among more than 15,000 patients examined in clinics nodules were found in 110 or about



Fig 35 Juxta articular nodules

7 per thousand Among . 159 of the patients who gave no history of infection with yaws who showed no other signs of the disease and whose serologic tests were negative there were only 3 cases of juxta articular nodules or about 1 4 per thousand patients In contrast among 13,314 patients who undoubtedly had yaws nodules were found in 107

intermediate zone of dense compact, fibrous tissue with relatively little cellular structure and (c) an inner zone of amorphous hyaline, collagenous material Spirochetes rarely have been demonstrated in juxta articular nodules either by silver staining or by animal inoculation[131 135]

Late Skin Lesions

The late skin lesions of yaws (Figs 37 and 38) are distinguished from secondary lesions by their characteristic clinical features by their time of appearance which is ordinarily late in the disease, and because of the



Fig 37 Late nodulo-ulcerative yaws

difficulty in demonstrating *T pertenue* in such lesions That late skin lesions often referred to as tertiary are a result of yaws has been disputed in the past by many who would assign the etiologic role to syphilis The circumstances of the history the evolution of the lesions the results of serologic tests and the prompt response to specific treatment leave no doubt that they represent a form of treponematosis That this is yaws and not syphilis is indicated by evidence of previous lesions of yaws in nearly all cases and by the frequency with which characteristic late

Grossly juxta articular nodules are fibrous tumors composed of hard greyish white tissue without a definite capsule with a poor blood supply and sometimes showing scattered opaque yellow spots of softening and necrosis Microscopically they consist of dense fibrous tissue with scattered foci of chronic inflammatory reaction of mononuclear cells lymphocytes and plasma cells Areas of necrosis are seen occasionally, and



Fig 36 Juxta articular nodules

Langhans' type of giant cells may be found but there is no tubercle formation Characteristically there may be three more or less well defined zones (a) an outer zone of loose fibrous structure with numerous fibroblasts and considerable mononuclear cellular infiltration (b) an

resulting lesion depends upon which type of change is predominant The lesions often are multiple, frequently associated with underlying bone involvement and may occur in any part of the body In the absence of treatment late lesions tend to be chronic with peripheral spread and central scarring This may be so extensive that a large portion of the integument is involved When hypertrophic changes predominate areas of induration or nodules, a few millimeters to a few centimeters in size, are formed in the skin or subcutaneous tissue giving the area a raised knobby appearance The lesions may spread peripherally forming arcuate borders with gradual disappearance of the changes in the center



Fig 39 Late nodulo ulcerative syphilis Photograph supplied by Dr Harry M Robinson

The latter usually shows some residual atrophic scarring and either an increase or decrease in pigment As a rule there is necrosis of the central portion of one or more nodules resulting in ragged punched out ulcers which may coalesce to form a deep spreading ulceration This type of late lesion was well described by Moss and Bigelow[11] These nodules are thickly studded and regularly set over an area 8 to 10 cm in diameter The size of the area involved increases by an advancing margin consisting of an almost unbroken row of nodules healing takes place in the center of the area the nodules frequently under-

lesions are found in population groups among whom yaws is prevalent while syphilis is rare. Late lesions usually do not appear until several years after the primary lesion but an occasional case may be seen in which late ulcerative changes are found while typical infectious papules are still present. It is possible that at times persisting early types of lesions may merge gradually into the late type[25], although Hackett[12]



Fig 38 Late ulcerative yaws

stated that the late destructive lesions always follow the secondary eruption usually after a symptom free interval of several years.

The changes in late skin yaws may be hypertrophic or destructive both processes often occurring together, and the appearance of the

resulting lesion depends upon which type of change is predominant. The lesions often are multiple frequently associated with underlying bone involvement and may occur in any part of the body. In the absence of treatment late lesions tend to be chronic with peripheral spread and central scarring. This may be so extensive that a large portion of the integument is involved. When hypertrophic changes predominate areas of induration or nodules, a few millimeters to a few centimeters in size, are formed in the skin or subcutaneous tissue giving the area a raised knobby appearance. The lesions may spread peripherally forming arcuate borders with gradual disappearance of the changes in the center



Fig 39 Late nodulo ulcerative syphilis Photograph supplied by Dr Harry M Robinson

The latter usually shows some residual atrophic scarring and either an increase or decrease in pigment. As a rule there is necrosis of the central portion of one or more nodules resulting in ragged punched out ulcers which may coalesce to form a deep, spreading ulceration. This type of late lesion was well described by Moss and Bigelow[121] 'These nodules are thickly studded and regularly set over an area 8 to 10 cm in diameter. The size of the area involved increases by an advancing margin consisting of an almost unbroken row of nodules ... healing takes place in the center of the area ... the nodules frequently under

went ulcerative changes varying from very superficial ulcerations involving the individual nodules to extensive and deep ulceration which sometimes become confluent over large areas of the body The degree and character of the resulting scarring probably depends upon the depth to which the ulceration had extended Sometimes there remains only an increase in pigmentation, sometimes the skin over the entire area involved was left thin and crinkly Again, where the ulceration has extended to a greater depth there may result complete leucoderma and sometimes painful keloid



Fig 40 Late syphilis predominately ulcerative Photograph supplied by Dr Harry M Robinson

In the predominately ulcerative destructive type of lesion there may be no evidence of nodulation and the appearance is that of an indolent irregular, jagged ulcer with steep edges and a necrotic base At times regular round or oval ulcers with a punched out appearance are formed, varying in size from one to several centimeters in diameter These lesions, which often develop on the lower legs, frequently are difficult to distinguish from what have been called tropical ulcers of unknown etiology Secondary infection with pyogenic and saprophitic organisms may play a part in producing and perpetuating ulcerative lesions

Another type of late skin lesion with little or no nodulation or ulceration was seen occasionally in Jamaica This was characterized chiefly by oval or circular patches of scaling thickened skin, at times there were small papules in the advancing border Frequently these lesions assumed an annular configuration with evidence of central heal ing and scarring Loss of pigment was a common feature Often various types of late skin lesions are found in the same patient

Serologic tests are strongly positive in patients with late skin lesions of yaws Response to specific treatment usually is prompt in the nodular non destructive type but it may be slow in the ulcerative type of lesions particularly those on the lower extremities

An example of the nodular late lesion with ulceration is shown in Fig 37 A predominantly destructive lesion is shown in Fig 38 On a purely morphological basis late yaws skin lesions cannot be distinguished from the nodular ulcerative gummas of late syphilis which are illus trated in Figs 39 and 40

Tenosynovitis or Ganglion

It has long been known that cystic swellings about the tendon sheaths are associated with yaws Hermans, who classified ganglions as a ter tiary yaws lesion referred to an article published in Dutch in 1780 which mentioned swellings of the tendons and their coverings among framboesia patients He stated that ganglions are seen usually on the back of the hand where a hard mass is formed which moves with the tendons They may occur in other locations such as the dorsum of the foot or behind the malleoli MacGregor described 50 cases of ganglion about the wrist associated with positive serologic tests in Nigeria where yaws is prevalent In a number of cases multiple ganglia were present and in two cases the feet were involved[13] In Uganda Hackett found ganglion in of 119 patients classed as cases of tertiary yaws Findlay reported that ganglion was very common in native troops in West Africa where 68 cases of ganglion including two on the dorsum of the foot were found among 60 477 African soldiers admitted to hospital a rate of about 1 1 per 1 000 admissions Among more than 16 000 European troops (among whom yaws must be very rare) hospitalized in the same area there were only two admissions for ganglion or 1 2 per 10 000 admissions[1 2] In Jamaica ganglia were seen in about 4 per thou sand yaws patients of all types and about half as frequently among

patients who were believed not to have yaws[69, 88] However, in the latter group there were doubtless many who had the disease, but in whom a diagnosis could not be made because of lack of historical, clinical or serologic evidence of previous infection

Clinically tenosynovitis is believed to be a late manifestation of yaws, occurring commonly when the disease otherwise is latent, although there may be other late manifestations of infection Serologic tests usually are positive Ganglia are painless cystic swellings usually rounded or oval irregularly lobulated They may attain a size of 8 to 10 cm in the greatest diameter and an elevation of 2 to 4 cm, although the majority measure about 1 to cm Although not attached to the skin, they are adherent to deeper structures and frequently move with underlying tendons A number of ganglia excised by the author in West Africa proved to be lobulated sacs arising either from tendon sheaths or bursae There were numerous fine trabeculae extending from the wall of the sac to the tendons The cystic sacs were filled with a semi fluid, clear, gelatinous material In most cases seen in Jamaica the swellings diminished in size or disappeared completely within a few weeks of starting treatment with neoarsphenamine or bismuth salicylate, although in some no response to treatment was observed

Ocular Lesions

Lesions of the eye apparently are extremely uncommon Occasionally conjunctivitis may be observed during the secondary eruption when yaws papules develop on the margin of the lids Hermans[1] referred to a rare case in which iritis was reported and Castellani and Chalmers[16] described two typical cases of iritis observed during the general granulomatous eruption with symptoms of photophobia ciliary congestion and discoloration of the iris In contrast, iritis is a common manifestation of secondary or relapsing early syphilis This type of ocular lesion was found in 6 8 per cent of 1 614 Baltimore negroes with secondary syphilis but in none of 269 Jamaicans with secondary yaws[138] According to Frazier iritis occurs about twice as frequently among negroes as among whites with early syphilis No reports of interstitial keratitis in yaws have been found although this complication is relatively common in late congenital syphilis Several children with stigmata of congenital syphilis including interstitial keratitis were seen in Kingston Jamaica where syphilis was not uncommon and yaws was rare[109], but interstitial

keratitis was not noted among many thousand children observed in rural areas Matsumoto[31] stated that in experimental yaws in rabbits keratitis frequently develops during the stage of generalization of the infection and that spirochetes can be demonstrated in the cornea

Lesions of Testis and Epididymis

Although the testicle is involved frequently in syphilis reports of testicular yaws are rare Stokes stated that the testis is involved in syphilis nearly as often as the bones and the skin although slight degrees of syphilitic orchitis are often overlooked because of failure to palpate the contents of the scrotum[13] Hazen reported that syphilis of the testicle (frequently found at autopsy) is commoner in negroes than in whites[141] In yaws there is little information on the incidence of involvement of testis and epididymis Only rare references to such lesions are found in the literature probably because involvement of these structures has not been looked for Hermans[1] cited only one reference which describes a case of gumma of the testis Among more than a thousand yaws patients in Jamaica suspicious lesions of testis or epididymis were found in only three In one a child 9 years old there were numerous late ulcerative skin lesions the left testis was twice the size of the right and the lower half was occupied by a hard nodule Another case was that of a 15 year old boy with secondary skin and bone lesions the left testis showed a firm irregular painless swelling The third patient was an infant 2 years old who had yaws for only a month His right testis was enlarged to twice normal size It was firm irregular and painless In the epididymis were several small granules[96]

Cardiovascular Lesions

In most clinical descriptions of yaws cardiovascular lesions are seldom mentioned and many observers have stated categorically that the cardiovascular system is not affected However one of the criteria frequently used for differentiating between yaws and syphilis is the absence of cardiovascular lesions in yaws According to such reasoning if a patient has positive serologic tests with or without gummatous lesions of skin or bones and in addition shows evidence of aortitis or aneurysm yaws is excluded because of the evidence of vascular damage

and a diagnosis of syphilis is made regardless of whether there was a history of infection with yaws in the past. This type of argument does not serve to clarify the relationship between the two patterns of treponematosis but rather confuses the issue, because it establishes a limiting definition of yaws as a disease which must not cause vascular lesions.

A complete study of a yaws population, among whom syphilis is absent, should serve to establish the frequency with which cardiovascular lesions are the result of yaws. Unfortunately there is probably some syphilis in any group and cases of aortitis or aneurysm might be due to syphilis rather than to yaws.

Harper stated that while tabes, paresis and aneurysm were well recognized as sequelae of syphilis, they had apparently been overlooked as a late manifestation of yaws. Yaws was said to be universal in Fiji, while syphilis was unknown, but numerous cases of tabes, paresis and aneurysm were seen by Harper among 6 000 Fijians[110]. Hunt and Johnson mentioned one case of aneurysm in 000 cases of yaws treated in American Samoa where syphilis presumably did not exist[121].

Choisser[141] described a series of 700 consecutive autopsies performed in a large general hospital in Port au Prince, Haiti, which admits patients from all parts of the Island where both syphilis and yaws are very common. More than 65 per cent of the autopsied cases had given a clinical history of infection with either syphilis or yaws. Aortic aneurysm was found in 8 cases which were classified as yaws and not syphilis. The pathological processes found in the definite yaws cases were identical with those found in routine cases of "treponematosis" representing either yaws or syphilis. The pathological evidence of yaws consisted of degeneration and scarring of the intima of the aorta beginning about 5 millimeters above the aortic cusps and extending upward around the aortic arch in some cases. In later stages the entire aorta sometimes presented a picture of extensive atheromatous degeneration with ulceration in some instances. Choisser's conclusions are open to criticism because syphilis as well as yaws was common in Haiti, and it is not possible to be certain in any given case that yaws and not syphilis was the infection responsible for observed lesions[141].

Weller[14] examined a group of 169 aortas from autopsy material from the Haitian General Hospital at Port au Prince. A large proportion of the cases from which the material was obtained had either yaws or syphilis or both according to the clinical histories and the presence of characteristic scars. Nearly two thirds of the aortas showed histologic lesions which could not be differentiated from those found as a result

of syphilis in the temperate zone The changes frequently extensive and marked included perivascular round cell infiltration in the adventitia and media fibrous and hyaline changes in the aortic intima necrosis and active cellular infiltrations in the media sometimes definitely gummatous and caseating destruction of the elastica of the media with hyaline fibrosis and scar formation and all stages in the formation of aneurysm Special staining revealed spirochetes morphologically *T pallidum* or *T pertenue* in 30 per cent of 97 cases The author concluded that either yaws and syphilis are essentially the same disease or the group of patients here considered had such a high incidence of syphilis that the evidences of this disease are overwhelmingly obtrusive or yaws and syphilis if different diseases produce identical aortic lesions adding still another item to the list of indistinguishable attributes of the two conditions [112]

Harley[113] analysed the clinical findings in a random sample of 3,597 patients who came to his dispensary in the Liberian hinterland He found the majority of the natives infected with yaws and while nearly every child had secondary framboesides venereal syphilis was not seen It is probable that most of the patients had yaws and not syphilis because the great majority had lesions common in yaws more than [illegible],000 of them had skin granulomata ulcers and scars more than 2,000 had various types of bone lesions chiefly periostitis and about 1,600 showed plantar palmar dermatitis Harley found clinical evidence of aneurysm in 6 cases and of aortic valvular disease in [illegible] cases a total incidence of about 5 cases of obvious vascular disease per thousand patients This incidence is probably low because the observations were made under field conditions by a pioneer missionary without the benefit of the time or the equipment necessary for more refined clinical and laboratory examinations If detailed clinical laboratory and post mortem examinations had been possible many more cases of cardiovascular disease might have been found Concerning the relationship of yaws and syphilis to these lesions Harley stated I believe that these records deal with one — not two — diseases If our present terminology is worth anything I must call it yaws It is quite possible that someone else would call it syphilis and let it go at that [113]

Wilson[114] recorded the clinical findings in nearly 500 cases of yaws in Panama and 1,500 in Haiti Hemiplegia (cerebral hemorrhage or thrombosis) in persons less than 40 years of age was noted in 3 patients in Panama and in 4 patients in Haiti aneurysm was seen once in Panama and three times in Haiti He believed that hemiplegia could not be

attributed to syphilis because of the absence of genital scars or of a history suggesting infection whereas all give a history of infection with yaws many years before the onset of paralysis All four cases with aneurysm had had yaws in childhood all had positive serologic tests and three had scars suggestive of healed yaws lesions These three denied any signs or symptoms suggesting syphilis but the fourth patient gave a history of having a transient small boil on the shaft of the penis which discharged pus for a few days and healed in a week without treatment One patient a boy 15 years old who had yaws in infancy revealed on x-ray examination a large pulsating tumor blending into the supracardic density One patient was a girl of 18 who had yaws as a child, roentgenograms revealed a widely dilated aorta' She died three days after examination from a massive hemorrhage from the mouth The third patient was a man of twenty one who had both yaws as a small boy and a penile sore when he was nineteen He also died a short time after examination and autopsy revealed a large ruptured aneurysm of the abdominal aorta The fourth case was a man 65 years old who had yaws when he was seven When examined he showed a scar at the site of the primary yaws lesion a pulsating tumor in the suprasternal notch present for two years, tracheal tug and symptoms of hoarseness cough and pain in chest

Wilson believed that yaws rarely may be the etiologic factor in aneurysm but that if *T pertenue* and *T pallidum* are identical one would expect to find a much higher incidence of aneurysm where yaws is prevalent particularly since the population affected are mainly negroes His observed incidence of aneurysm was about 2 per thousand yaws cases[111]

As a group yaws patients seen in Jamaica were remarkably free from signs or symptoms of cardiovascular disease[98] Turner recently has analysed additional data from Jamaica which is shown in Table III[11] Among a group of [illegible],88 yaws patients representing all age groups and all stages of the disease x rays in addition to clinical examinations were made in 5[illegible]0 patients Evidence of cardiovascular disease confirmed by x ray examinations was found in 18 patients In 14 the lesions were classed as questionable consisting for the most part of dilatation of the aortic arch greater than would be expected on the basis of the patients ages In the remaining 4 patients clinical or x ray evidence indicated definite cardiovascular disease of the type found in syphilis Two had aortic insufficiency, and two had aortic aneurysm Studies were made

TABLE III

RESULTS OF CARDIOVASCULAR EXAMINATIONS OF YAWS AND NO YAWS PATIENTS

Age Groups in Years	YAWS: Clinical Examination Only All Negative	YAWS: None	YAWS: Clinical Examination Plus X Ray Abnormalities: Questionable	YAWS: Clinical Examination Plus X Ray Abnormalities: Definite	YAWS: Total	NO YAWS: Clinical Examination Only All Negative	NO YAWS: None	NO YAWS: Clinical Examination Plus X Ray Abnormalities: Questionable	NO YAWS: Clinical Examination Plus X Ray Abnormalities: Definite	NO YAWS: Total
0 19	1325	6	0	0	1331	694	1	0	0	695
0 39	748	285	0	2	1034	302	41	0	0	343
40 59	227	168	8	1	404	110	74	0	0	193
60 and over	61	43	6	2	113	32	21	6	0	59
TOTALS	2362	502	14	4	2882	1147	137	6	0	1 90

in a control group of 1 90 patients who showed no clinical or laboratory evidence of yaws X ray in addition to clinical examination were performed in 143 of them among whom there were 6 who showed questionable and none who showed definite evidence of cardiovascular lesions of the syphilitic type There is seen to be little difference in the frequency of questionable lesions which is about 5 per thousand people in each group However it is probably significant that all 4 patients with definite vascular damage were in the "yaws" group, while not one occurred in the no yaws group On the basis of chance alone there is probably no statistically significant difference but when the immunologic relationship of yaws and syphilis is considered, the difference of the frequency of cardiovascular lesions in the two groups becomes more important There is no doubt that infection with yaws affords a measure of protection against syphilis and patients with yaws should be much less likely to have syphilis than those who had never had yaws Therefore, if syphilis were the cause of the aneurysms and other aortic lesions it would be expected that patients with such lesions would be found in the "no yaws group In Turner's Jamaican material there was another group of individuals designated as no yaws history positive serology", patients living in yaws areas who gave no clinical history of infection with yaws and who showed no definite signs of the disease except positive serologic tests This group accounted for about 6 per cent of the total population in two rural communities It is reasonable to suppose that the majority of this group had yaws and not syphilis because yaws was 100 times as common as syphilis yaws prevalence being about 50 per cent while that for syphilis was only about 0 5 per cent [8] Among the patients with positive serologic tests in the absence of a history of yaws infection there were four additional patients with definite cardiovascular lesions of the syphilitic type Two of them had aortic regurgitation and two had aortic aneurysm It is not possible to be certain whether yaws or syphilis was responsible for the vascular lesions, but all had spent their lives in epidemic yaws areas and it is probable that they were infected with yaws rather than syphilis

The data on the occurrence of obvious cardiovascular lesions from four different sources is summarized in Table IV It can be seen that the observed frequency of aneurysm or of aortic valvular lesions varies from 0 5 to 5 0 per thousand yaws population the mean being 3 0 per thousand It is probable that the figures do not represent the actual prevalence of such lesions because they represent only those which are readily

detected by clinical examination. Only in the Jamaican series were x-ray examinations included in any number of patients.

There is a marked contrast between the rarity of cardiovascular damage in yaws patients and the frequency with which such lesions are found in persons with syphilis. It is generally accepted that syphilitic aortic disease occurs in about 10 per cent of syphilitics of all races[139, 146] and it is well known that syphilitic cardiovascular lesions occur with much greater frequency in negroes than in whites[140, 146]. On the basis of a frequency of 10 per cent the expected number of persons with aortic lesions in a yaws population numbering more than 1[illegible],000 would be about 1[illegible]0 cases if yaws produced such lesions as frequently as syphilis. However, if the racial factor is considered, the yaws population being largely negro, the expected number of cases would be much greater, possibly 200 or more or five or six times the observed number.

TABLE IV

SUMMARY OF DATA ON THE OCCURRENCE OF OBVIOUS CARDIOVASCULAR LESIONS (ANEURYSM OR AORTIC VALVULAR DISEASE) IN YAWS POPULATIONS

Author	Reference Number	Location	Number of Yaws Cases	Number with Obvious Cardiovascular Lesions	Rate Per 1,000
Hunt and Johnson	131	Samoa	[illegible]00	1	0.5
Harley	143	Liberia	5,597	28	5.0
Wilson	144	Haiti and Panama	2,000	4	2.0
Turner	145	Jamaica	882	4	1.4
TOTAL			1[illegible]4[illegible]9	37	3.0

Not all had yaws

There appears to be little doubt that yaws can and does affect the vascular system, causing lesions which are clinically and histologically identical with those caused by syphilis, but occurring much less frequently. The reasons for the difference in prevalence in the two types of treponematosis are not clear. It has been suggested that a marked secondary reaction in yaws or syphilis affords protection against serious late sequelae. It is possible that late visceral lesions in yaws are rare because the disease is characterized by a much more profuse early skin eruption and more marked and widespread bone lesions than syphilis. However, this theory falls down when applied to the relative frequency of cardiovascular lesions in syphilis in negroes and whites. Negroes who characteristically react to early syphilis with more marked and

proliferative early skin and bone lesions than whites, also suffer more often from late cardiovascular syphilis

There is apparently an inverse ratio between the occurrence of benign late syphilis and cardiovascular syphilis Frazier and Li[1] stated that in persons with tertiary syphilis, if the infection produces clinical disease in cutaneous and skeletal structures, it does not, as a rule, produce demonstrable disease in the heart and great blood vessels, although in the negro race 21 per cent of patients with skeletal disease also had cardiovascular lesions Late destructive lesions of the skin and the skeletal system are very common in yaws which may have a bearing on the rarity of demonstrable cardiovascular disease

Neural Lesions

Invasion of the nervous system by *T pertenue* with the production of clinical or laboratory evidence of disease has long been a controversial point There is no doubt that spirochetemia occurs early in the disease and the organisms must be widely disseminated throughout the body It is hardly possible that the nervous system is spared entirely and accumulating evidence indicates that yaws sometimes causes damage to neural structures As in the case of cardiovascular involvement the school of thought which denies that yaws plays a causal role would exclude yaws as a contributing factor and maintain that syphilis must be the cause of syphilis like lesions of the nervous system For example Cook who studied the incidence of neuro syphilis in Trinidad where yaws is endemic used the following criteria to make a diagnosis of yaws and to exclude syphilis typical florid lesions of yaws a history of treatment for yaws in childhood with the presence of typical scars a low titer serologic test and a normal cerebrospinal fluid In other words any patient with positive serologic tests and with abnormal cerebrospinal fluid tests was automatically excluded from the yaws group and classed as syphilitic[147]

The opposing view, that yaws may damage the nerve tissue in a way similar to syphilis is supported by considerable epidemiologic clinical and laboratory evidence If it is accepted that a certain measure of protection against syphilis is afforded by a previous infection with yaws then it must follow that in a given population group syphilis would occur with less frequency in that segment of the population which had suffered from yaws than in the remainder Therefore if syphilis-like

lesions of the nervous system result only from syphilis and not from yaws their frequency should be greater in the segment of the population which had no yaws However such is not the case for available statistical material indicates that syphilis like neural lesions occur with greater frequency in the yaws infected than in those without yaws among populations where the disease is prevalent

Harper saw numerous cases of tabes and paresis in Fiji where he said syphilis was non existent[110] Harley noted signs of spastic paraplegia in 29 and of tabes in 14 persons among 5 597 patients most of whom had other signs of yaws[113] Wilson described 7 cases of hemiplegia in young adults in Panama and Haiti which he felt were the result of yaws and not of syphilis[111] Choisser found at autopsy 3 instances of spontaneous intracranial hemorrhage in young adults who gave histories of having yaws in childhood whose serologic tests were positive and who had received no specific therapy[111]

In Jamaica treatment teams of the Yaws Commission carried out control measures in rural areas with a population of about 57 000 House to house and person to person surveys were made by trained yaws inspectors who were instructed to include in their data reports on any person with obvious paralysis of any type The great majority of these paralytics were studied later in clinics by physicians and in many the cerebrospinal fluid was examined[99] On the basis of survey findings and data from other areas of Jamaica[98] the population may be classified according to their yaws status as follows yaws, past or present in about 56 per cent or 32 000 no history or signs of yaws but serologic tests positive in about 6 per cent or 3 400 and no evidence of yaws in about 38 per cent or 1 600 Neurological lesions of the type commonly caused by syphilis were found in the yaws segment of the population in 54 persons or 1 7 per thousand in the no yaws group in only 2 persons or 0 1 per thousand and in the group with no historical or clinical evidence of yaws but with positive serologic tests in 9 persons or ~7 per thousand The distribution and type of neurological lesions is given in Table V It is evident that in Jamaica at least syphilis like neurologic lesions occurred in the yaws group with a frequency seventeen times greater than that in the group who did not have yaws Because yaws is extremely common and syphilis is rare in rural Jamaica it is probable that in the group without a definite history or other sign of yaws serologic tests were positive because of yaws and not because of syphilis in the majority and that this segment might be added to the yaws group

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In that case there would be 63 cases with neurologic lesions or about 1 8 per thousand

The material from Jamaica probably is representative of the types of clinical neurologic abnormalities found in populations suffering from yaws The cases were principally hemiplegia paraplegia and less frequently tabes or paresis

Hemiplegia was the diagnosis in 22 patients with yaws and in 3 others whose serologic tests were positive in the absence of a history or other evidence of the disease In the yaws group paralysis developed before 30 years of age in 7 patients between 30 and 40 years of age in another 7 patients and after 40 years of age in the remaining 8 It is not suggested that the hemiplegia resulted in each case from yaws for it is well known that other factors are important in causing cerebral vascular accidents due to hemmorrhage thrombosis or embolism but it probably is significant that hemiplegia occurred in the yaws population with a frequency 7 times that in the no yaws population and that many patients were young adults The average duration of yaws before the onset of paralysis was 9 years ranging from 6 to 6 years In 5 cases the duration was more than 40 years Among 17 of the cases of yaws and hemiplegia blood pressure readings were normal in 1 and definitely elevated in 5 Serologic tests were positive in 15, negative in 5 and not recorded in 2 The spinal fluid was examined in 13 cases with the following results the fluid was normal in 9 cases and abnormal in 4 the abnormalities consisting of a positive complement fixation test in 3 a positive Pandy test in 2 and an abnormal colloidal mastic test in 1

In the group with no history of yaws but with positive serologic tests there were 3 patients with hemiplegia Two of these patients were more than 50 years old and had marked hypertension the other was a woman 31 years of age who had a stroke when she was 18 Her blood pressure and spinal fluid were normal

Spastic paraplegia was observed in 19 patients with yaws and in others who had positive serologic tests in the absence of other evidence of yaws or syphilis except in one man who had had a penile lesion All the patients had definite spastic paralysis of the lower extremities and in some there was spasticity of one arm Paralysis developed before 0 years of age in 2 patients between the ages of 0 and 30 years in 5 patients between 30 and 40 years in 6 patients and after 40 years of age in the remaining 6 The average duration of yaws before the onset of neurologic symptoms was 23 years ranging from to 49 years Blood pressure readings recorded in 10 patients were all normal Serologic

TABLE V

NUMBER OF CASES OF CERTAIN TYPES OF NEUROLOGICAL LESIONS SEEN IN JAMAICA RELATED TO YAWS STATUS

DIAGNOSIS—YAWS STATUS

Type of neurological lesion found on clinical examination	*Yaws (3 000)*		*No Yaws History Serology Positive (3 400)*		*No Yaws History Serology Negative (1 600)*		*Total (57 000)*	
	Number	*Rate per 1000*	*Number*	*Rate per 1000*	*Number*	*Rate per 1000*	*Number*	*Rate per 1000*
Hemiplegia	22	0 7	3	0 9		0 1	27	0 5
Spastic Paraplegia	19	0 6	2	0 6	0	0	21	0.4
Tabes	9	0 3	4	1 2	0	0	13	0
Paresis	4	0 1	0	0	0	0	4	0 07
Total	54	1 7	9	7	2	0 1	65	1 1

In that case there would be 63 cases with neurologic lesions or about 1 8 per thousand

The material from Jamaica probably is representative of the types of clinical neurologic abnormalities found in populations suffering from yaws The cases were principally hemiplegia paraplegia and less frequently, tabes or paresis

Hemiplegia was the diagnosis in 22 patients with yaws and in 3 others whose serologic tests were positive in the absence of a history or other evidence of the disease In the yaws group paralysis developed before 30 years of age in 7 patients between 30 and 40 years of age in another 7 patients and after 40 years of age in the remaining 8 It is not suggested that the hemiplegia resulted in each case from yaws for it is well known that other factors are important in causing cerebral vascular accidents due to hemorrhage thrombosis or embolism but it probably is significant that hemiplegia occurred in the yaws population with a frequency 7 times that in the no yaws population and that many patients were young adults The average duration of yaws before the onset of paralysis was 9 years ranging from 6 to 6- years In 5 cases the duration was more than 40 years Among 17 of the cases of yaws and hemiplegia blood pressure readings were normal in 1 and definitely elevated in 5 Serologic tests were positive in 15 negative in 5 and not recorded in - The spinal fluid was examined in 13 cases with the following results the fluid was normal in 9 cases and abnormal in 4 the abnormalities consisting of a positive complement fixation test in 3 a positive Pandy test in 2 and an abnormal colloidal mastic test in 1

In the group with no history of yaws but with positive serologic tests there were 3 patients with hemiplegia Two of these patients were more than 50 years old and had marked hypertension the other was a woman 41 years of age who had a stroke when she was 18 Her blood pressure and spinal fluid were normal

Spastic paraplegia was observed in 19 patients with yaws and in others who had positive serologic tests in the absence of other evidence of yaws or syphilis except in one man who had had a penile lesion All the patients had definite spastic paralysis of the lower extremities and in some there was spasticity of one arm Paralysis developed before 20 years of age in 2 patients between the ages of 20 and 30 years in 5 patients between 30 and 40 years in 6 patients and after 40 years of age in the remaining 6 The average duration of yaws before the onset of neurologic symptoms was 3 years, ranging from to 49 years Blood pressure readings recorded in 10 patients were all normal Serologic

TABLE V

NUMBER OF CASES OF CERTAIN TYPES OF NEUROLOGICAL LESIONS SEEN IN JAMAICA RELATED TO YAWS STATUS

DIAGNOSIS—YAWS STATUS

Type of neurological lesion found on clinical examination	*Yaws (3 000)*		*No Yaws History Serology Positive (400)*		*No Yaws History Serology Negative (1 600)*		*Total (5 000)*	
	Number	*Rate per 1000*	*Number*	*Rate per 1000*	*Number*	*Rate per 1000*	*Number*	*Rate per 1000*
Hemiplegia	22	0 7	3	0 9		0 1	27	0 5
Spastic Paraplegia	19	0 6		0 6	0	0	1	0.4
Tabes	9	0 3	4	1	0	0	13	0
Paresis	4	0 1	0	0	0	0	4	0 07
Total	54	1 7	9	2 7	2	0 1	65	1 1

to the usual tests Hematologic studies showed no evidence of primary anemia

Four patients who denied infection with yaws but whose serologic tests were positive were classed as tabetic Two were women 26 years old who had had difficulty in walking for about a year Both were ataxic with absent deep reflexes in the lower extremities and in one the pupils failed to react to light The spinal fluid was normal in the first case and abnormal in the other with a positive complement fixation reaction and an abnormal mastic curve One patient a man of 35 who had complained of weakness in his legs and difficulty in walking for 2 years showed a typical tabetic gait and absent deep reflexes in his legs but his pupils reacted normally, and his spinal fluid was normal The fourth patient a man of 56 who gave a history of a hard penile sore followed by a skin rash 37 years earlier while living in one of the larger towns of Jamaica complained of incontinence His reflexes were normal but his spinal fluid gave a positive complement fixation reaction and an abnormal mastic curve

A diagnosis of paresis was made in 4 persons, all of whom had yaws The age at onset of neurological symptoms was between 30 and 40 years in 3 patients and between 40 and 50 years in the others The average duration of yaws at that time was 34 years ranging from 30 to 40 years All showed spasticity and trembling of the legs and mental deterioration and Argyll Robertson pupils were observed in Serologic tests were positive in 2 and negative in 2 while the spinal fluids showed some abnormality in all One showed only a positive Pandy test One showed a positive Pandy test 15 white cells per cubic mm a positive complement fixation test in amounts of 0 1 c c or more and an abnormal mastic curve One showed a positive complement fixation test and an abnormal mastic curve and one showed 160 cells per cubic mm 90 per cent lymphocytes, a positive Pandy test positive complement fixation in all amounts and a first zone mastic curve

One paretic gave a history of having yaws in childhood and a penile sore in early adult life He had aortic regurgitation in addition to paresis Syphilis may have been the cause of the neurologic and cardiovascular lesions in this patient In fact it is impossible to rule out syphilis in any of this group of patients but all gave a definite history of infection with yaws in childhood all had spent their lives in rural Jamaica where syphilis is rare and yaws is common and only one patient gave a history which suggested infection with syphilis.

One patient a 46 year old negro entered the clinic complaining

tests were positive in 12, negative in 6 and not recorded in 1 patient Spinal fluid was examined in 15 cases In 10 the fluid was entirely normal in 5 there were various degrees of abnormality Complement fixation tests were positive in 3, in 1 case there were 14 leucocytes per cubic mm of fluid and in 1 only an abnormal colloidal mastic test was found

Certain clinical features of some of this group of patients are of interest One who gave positive complement-fixation tests in both blood and spinal fluid showed destruction of the nasal septum Another presented late ulcerative skin lesions of yaws with bone involvement, and one had plantar hyperkeratosis and scaling An additional patient, a girl of 16 who had become paralyzed in the legs at about 13 years of age and who had had yaws several years previously had to be carried into the clinic Examination revealed spastic paralysis of the lower extremities a weakly positive blood Wassermann reaction and a normal spinal fluid Treatment with a course of 6 weekly injections of neoarsphenamine was followed by rapid improvement, and in 6 months she was walking without assistance

Of the 2 patients with spastic paraplegia and positive serologic tests but with no history or signs of yaws one was a man of 26 who gave a history of having a penile sore 3 years earlier for which he had been given an undetermined amount of intravenous therapy He had had increasing difficulty in walking for about one year His spinal fluid was normal The other patient a woman of 45 had paralysis of her legs for several years Her spinal fluid showed only an abnormal colloidal mastic curve

A group of patients was classified as probably tabetic because of the presence of the usual signs of this disease Ataxia with a positive Romberg s sign and absent patellar and Achilles reflexes were found in all but one, and in several the pupils were small, did not react to light but did on accommodation

In the yaws group were 9 patients with probable tabes All were ataxic with absent deep reflexes in the lower extremities but in only 2 were Argyll Robertson pupils demonstrated The onset of disability occurred between 20 and 30 years of age in 3 patients between 30 and 40 in 5 and between 40 and 50 years of age in one The average duration of yaws before onset of neural symptoms was [illegible]4 years ranging from 8 to 40 years Blood Wassermann reactions were positive in 5 and negative in 4 cases Spinal fluids from 7 patients were all normal

to the usual tests Hematologic studies showed no evidence of primary anemia

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One patient a 46 year old negro entered the clinic complaining

of increasing stiffness and weakness in his legs for about 8 years He gave a definite history of florid yaws at 7 years of age which healed after several months without treatment He had had gonorrhea several times when a young man but never a penile sore or injection treatments He had always lived in the same rural area where yaws was very prevalent For about 8 years previous to admission he had noticed increasing stiffness and weakness in his legs and to a lesser extent in his arms He had had some difficulty in walking and talking, and for 2 years he had been emotionally unstable laughing and crying at slight provocation Physical examination revealed a large well-developed and nourished negro, who walked with a tremulous, spastic gait There was great speech difficulty and he slurred and fumbled his words His face and tongue were tremulous He was well oriented but emotionally unstable and wept during the examination Patellar and biceps reflexes were hyperactive but there was no ankle clonus, and the Babinski test was normal There were no gross sensory changes Pupils were irregular but reacted well Extra ocular movements were normal and fundu scopic examination revealed nothing of note His blood Wassermann reaction was positive The spinal fluid was under normal pressure clear, but the Pandy test was strongly positive there were 15 mononuclear cells per cubic mm of fluid complement-fixation test was positive with amounts of 0 2 c c or more of fluid, and there was a first zone mastic curve

In only 4 of this group of 65 patients presenting syphilis like neurologic signs was a history obtained which suggested infection with syphilis One was a paretic who had yaws in childhood and a penile sore in adult life The sera of 2 patients gave positive serologic tests in the absence of a history of yaws one of them, a paraplegic, had a penile lesion . years before neurologic disability appeared, the other, a tabetic, also gave a history of a hard penile sore many years earlier The fourth patient a man 37 years old had a penile sore at about 22 years of age and developed hemiplegia 2 years later He denied yaws, and his serologic tests were negative The distribution of 3 out of 4 probable syphilitics occurring in that segment of the population which denied yaws infection was to be expected on the basis of the protective effect of yaws

The relative rarity with which yaws is followed by *clinical evidence* of damage to the nervous system is equalled by the scarcity of marked changes in the cerebrospinal fluid Although van der Schaar found some abnormality in about 24 per cent of spinal fluids from 129 cases of yaws,

he found no changes during the early florid stage of the disease[115] Fischer[119] observed no changes in the spinal fluid taken from patients with all stages of yaws but Hewer[83] found increased cell counts and total protein in 3 of .5 yaws patients in Southern Sudan Turner studied the cerebrospinal fluid from nearly 450 cases of yaws of all stages in Jamaica Fluids were classed as positive when there was fixation of complement in amounts of 0 5 ml or less and definitely abnormal findings in one of the other tests including cell count colloidal mastic and Pandy tests Fluids were classed as questionable when minor abnormalities were found such as a slightly increased cell count some precipitation in the mastic test or incomplete complement fixation with 1 0 ml of fluid (Turner[125]) Table VI which records the findings in

TABLE VI

RESULTS OF EXAMINATION OF THE CEREBROSPINAL FLUID OF PATIENTS WITH YAWS ACCORDING TO PROBABLE DURATION OF THE INFECTION

Probable Duration of Yaws in Years	*Normal*	*Spinal Fluid Findings* *Questionable*	*Positive*
Less than 5	128	8	1
5-9	44	2	0
10-19	89	2	3
20-29	76	1	5
30-39	53	1	0
More than 40	32	0	3
Total	4 2	14	12

this group shows that only 1. or .7 per cent of the fluids showed significant changes Furthermore in 137 cases of yaws of less than 5 years duration there was only one definitely abnormal spinal fluid In the selection group of 54 yaws patients already described who presented gross clinical evidence of neurologic lesions spinal fluids were examined in 39 cases In 26 cases all tests were normal while definite abnormalities were found in 13 or 33 per cent

Damage to neural structures apparently may result from infection with yaws in a very small proportion of cases much smaller than that from infection with syphilis It is probable that not more than 0 2 per cent of yaws cases develop clinically manifest neural lesions and that a comparable proportion will reveal definite cerebrospinal fluid abnormalities including positive complement fixation tests increased cell counts and total protein and abnormal colloidal tests In contrast in

syphilis it is estimated that from 10 to 30 per cent of cases show clinical neurosyphilis and that during early syphilis spinal fluid abnormalities are found in perhaps a third of the cases[10]

Not only the total frequency of neural involvement but also the relative frequency of the various clinical patterns in yaws and syphilis appears to differ The majority of cases of manifest neurosyphilis are paretic or tabetic while other types such as spastic paraplegia and those caused by vascular damage including hemiplegia, are found less frequently[10] In yaws on the other hand spastic paraplegia and hemiplegia accounted for the great majority of cases with obvious neurologic lesions in Jamaica and also in cases described by Harley in Liberia[113]

Serologic Tests

The various serologic tests for syphilis involving complement fixation or flocculation play an equally important part in the diagnosis and management of yaws Serologic tests are positive with the same frequency and intensity in yaws as in syphilis becoming positive during the primary stage of the disease, remaining positive during the secondary stage and during the first several years of latency, then gradually becoming negative over a period of many years even in the absence of specific therapy Tests are positive in practically all cases in which active lesions are found regardless of the duration of infection

The Kolmer modification of the Wassermann reaction begins to show partial fixation of complement during the third or fourth week of the primary stage and from the fourth to sixth weeks serologic tests are positive in the majority of cases In untreated cases with multiple skin lesion, either early or late, the Kolmer-Wassermann reaction shows complete complement-fixation with amounts of serum varying from 0 006 c c to 0 003 c c and in general, sera from patients with active bone lesions exhibit a higher titer than from any other group of yaws patients[38] Serologic tests in cases of yaws, uninfluenced by treatment, are positive in from 90 to 100 per cent of cases during the first few years, by the end of 10 years from 60 to 70 per cent are still positive, after 20 years from 40 to 50 per cent are positive, and over succeeding decades serologic evidence of infection slowly disappears In a group of several hundred seropositive yaws patients treated with several weekly injections of neoarsphenamine or bismuth salicylate serologic tests had reverted to negative within 18 months in nearly 60 per cent

Pathology

The structural changes in early and late skin lesions of yaws and the differences from and similarities to comparable lesions of syphilis have been described by numerous observers during the past few decades Articles by Williams[14] and by Ferris and Turner[15] review previous studies and describe additional material

The initial lesion of yaws if not superimposed upon a pre existing ulcer is similar structurally to the framboesiform type of generalized lesions Grossly there is a papular elevation of the skin with obvious proliferation of epidermis and marked downgrowth of epithelial strands Commonly there is ulceration of the surface which may be covered with a crust composed of fibrin and cellular debris Microscopically there is seen to be proliferation of the epidermis which is ulcerated in some areas marked hypertrophy of rete pegs with swelling and edema of the dermis extending below the papillary layer Marked cellular infiltration with lymphocytes and plasma cells is common and occasional areas of infiltration with polymorphonuclear leucocytes are seen Often focal areas of infiltration occur around blood vessels and hair follicles Occasional epithelioid cells and at times giant cells are observed and fibroblasts may be increased in number Frequently there appears to be an increase in the number of capillaries the endothelium of which may be somewhat swollen In the scaling macular and folliculo-papular lesions some thickening of the epidermis is found but great hypertrophy of the epidermal papillae is lacking Except for this the histological changes are essentially similar to those observed in framboesiform lesions There is the same type and location of cellular infiltration and the same proliferation of capillaries

Treponemata are found in the epidermis in the dermal papillae and in some cases they are seen scattered throughout the subpapillary layer They may be grouped about blood vessels or hair follicles and often are very numerous in areas of polymorphonuclear infiltration Ferris and Turner found no evidence of phagocytosis of spirochetes in their studies[15]

The changes observed in skin lesions of a comparable type and duration in early yaws and in syphilis are essentially the same differences which are observed being mainly quantitative Moore has stated that the basic microscopic appearance of all early syphilitic lesions of the skin is the same cellular infiltration with lymphocytes plasma cells and

leucocytes with the formation of epithelioid cells and occasional giant cells the proliferation of fibroblasts and dilatation of blood vessels and thickening of the intima Large raised papules show acanthosis with widening and elongation of the rete pegs[13] This description might well apply to the appearance of all early yaws lesions of the skin, although Williams[11] believes that the changes in and around the blood vessels are less marked in yaws with less endarteritis and periarteritis Ferris and Turner, who examined material from yaws and syphilis subjects in Jamaica compared the folliculo papular and squamous lesions of yaws with maculo papular and papular lesions of syphilis They found that the edema and exudation of lymphocytes and plasma cells were perivascular in both diseases occurring about the small capillaries chiefly in the subpapillary dermis Swelling of capillary endothelium was seen in both yaws and syphilis but in their material there were no conspicuous change in the arteries Proliferation of fibroblasts was essentially equal in the two diseases and giant cells were observed in both, although apparently they were found more frequently in syphilis[15]

Late skin lesions of yaws may be predominantly of the nodular variety, with nodules situated superficially or deep in the subcutaneous structures or predominantly ulcerative, although both types are com monly found together Histologic changes include hypertrophy of the epidermis with thickening of the surface epithelium and hyperplasia of the rete pegs in the skin overlying the nodules or at the edges of ulcera tions Scattered small areas of edema and infiltration with polymorpho-nuclear leucocytes are observed The dermis in the nodular type of lesion and beneath the intact epithelium around ulcerated areas shows edema of the papillary and sub-papillary tissues with cellular infiltration with round cells epithelioid cells and giant cells and proliferation of fibroblasts Occasionally definite tubercle formation is evident and there may be scattered areas of necrosis Swelling of the endothelium of capillaries is a finding common to both types of late skin lesions but thickening of the walls of the smaller arteries with narrowing of the lumen is found mainly in the ulcerative type of lesion Such changes are similar to those found in comparable lesions of late syphilis and although Williams[11] felt that probably there would be less change in the blood vessels in ulcerative lesions of late yaws than in those resulting from syphilis Ferris and Turner stated that histologic criteria for the differentiation of the cutaneous and subcutaneous lesions of yaws and syphilis are unreliable Treponemata are found rarely in the late skin lesions of yaws[3]

Treatment

The treatment of yaws has followed very closely the prevailing modes in the treatment of syphilis and when one therapeutic regimen has been found to be effective in syphilis usually it has been given a trial in yaws Before the use of the organic arsenicals, the bismuth compounds and more recently the antibiotics various preparations of mercury were the mainstay of therapy in treponematous disease for centuries Hans Sloan in 1707 made frequent mention of 'salivation' in the treatment of yaws and he described one patient 'a Negro a lusty fellow, was taken ill of the yaws He had not been long out from Guinea I fluxed him by unction in the corner of an outhouse '[1] Thomas Dancer in 1819 recommended as treatment for yaws a wholesome diet calomel, mercury by mouth or by inunction and lignum vitae (guaiac) He was probably the first to mention the use of heat in treatment treponematosis when he wrote A Negro at Grenada is said to have been very successful in curing the yaws by placing the patient in a cask with a pan of burning coals and thus sweating him twice a day' '[2]

In 1910 Strong stated that mercury or potassium iodide undoubtedly cause the eruption in yaws to subside He also described the local application to skin lesions of various preparations including corrosive sublimate phenol nitric acid copper sulfate silver nitrate tincture of iodine and a watery paste of bismuth subnitrate and mentioned curetting the local lesions'[3,4] This local therapy harks back to the days of the slave trade when attempts were made to heal yaws lesions by external applications and suggests that yaws was often considered as an infection localized to the skin This concept which persisted for many years even after it was known that the disease was a generalized infection was fostered by the miraculous cures apparently attained by a single injection of arsphenamine

Arsphenamine Ehrlich s 606' was first used in the treatment of yaws in 1910 In that year Nichols who commented on the tedium of the usual treatment of the disease with potassium iodide and mercury suggested the trial of 606 because it was effective in syphilis and in yaws infected rabbits'[15] Strong reported on the first use of arsphenamine in human yaws Twenty five cases were given single intramuscular injections of 0 3 to 0 4 gm Three or four days after treatment the granulomatous lesions began to heal and in the course of 10 to 20 days they had disappeared entirely No case showed relapsing lesions

during the 4 months following treatment A few years later Castellani[156] said that, although arsphenamine and neoarsphenamine were undoubtedly the specific drugs of choice, difficulties of administration and objections of patients to intravenous medication made it desirable to have some effective preparation which could be given by mouth He recommended a formula containing tartar emetic, sodium salicylate, potassium iodide sodium bicarbonate and water, which later was known as Castellani s mixture and was widely used in some areas with apparent suppression of active yaws lesions During the subsequent two or three decades many other preparations were used sporadically in the treatment of yaws including stovarsol acetylarsan and other organic arsenicals, some of which were given by mouth, but chief reliance continued to be placed on the arsphenamine preparations and on some of the bismuth salts Soon after mapharsen was introduced into syphilotherapy in 193 , it was used successfully in the treatment of yaws and after penicillin was first shown to be actively antisyphilitic, it was found to be apparently equally as active in yaws

The value of a drug in the treatment of yaws may be judged from its effect in causing rapid healing of lesions in effecting sero reversal and in the prevention of clinical relapse The toxicity cost and ease of preparation and of administration are also factors of importance, particularly where mass treatments are given in an effort to bring about community control Unfortunately for a long time after arsphenamine was introduced it and other similar preparations were considered to be curative in one or two doses because of the rapidity of healing of obvious lesions It was believed that yaws could be eradicated much more easily than syphilis and it was not until much later that careful follow up observations of both the clinical and serologic results made it evident that biologic cure of yaws probably required an amount of treatment equal to that necessary for the cure of syphilis In 19-2 Gutierrez said that Ehrlich s ambition of a therapia sterilans magna applied more to yaws than to syphilis and that yaws required less treatment and responded with more rapid healing of lesions than syphilis He noted about 95 per cent 'clinical cures of yaws cases treated with one or two injections of neoarsphenamine and observed for periods of 1½ to 3 months[157]

Goodpasture and De Leon were apparently the first to record observations on the titer of serologic tests in yaws before and after treatment They found that the complement fixing ability of serum from early secondary yaws cases was equal to the maximal found in syphilis Fol

lowing clinical cure of yaws by one or two intravenous injections of arsphenamine they observed that the Wassermann reaction gradually weakened over a period of several months and was negative within 6 months after treatment in 7 of 1. cases[1 5] In 19 5 Moss made follow up observation on more than 400 cases of yaws treated in the Dominican Republic 5 years earlier with one two or three injections of neoarsphenamine in doses ranging from 0 075 gm for infants to 0 6 gm for fully developed adults He concluded that about 50 per cent of the cases were clinically cured by one injection and that 3 injections increased the proportion of cures considerably Wassermann tests done on sera from 79 patients revealed that 45 per cent gave negative tests 5 years after treatment[1 9] Novarro recorded the results of Wassermann tests on sera from 101 yaws patients from 3 months to 3 years after treatment with 1 to 5 injections of neoarsphenamine in amounts of 0 075 gm for infants and 0 5 to 0 6 gm for adults Eighty six of the group were given only one or two treatments and in 80 of these serologic tests were made two or more years later It was found that 8 per cent of the entire group and 78 per cent of those who had only one treatment gave entirely negative Wassermann reactions[167]

The Jamaica Yaws Commission observed the results of treatment of yaws cases at intervals of about six months during a period of more than two and a half years after treatment with either neoarsphenamine or bismuth salicylate[6 86 60] Results of treatment were judged by the number of clinical failures as represented by relapsing lesions and by the proportion of cases showing serologic reversal from positive to negative Patients were given from 1 to 6 weekly injections of either preparation the average being about 4 treatments per patient

Neoarsphenamine was prepared and injected intravenously in the usual way except in the case of small infants who were given intra muscular injections Each dose was graded according to body weight infants less than ten pounds in weight were given 0 05 gm and the dose was increased by 0 05 gm for each additional 10 pounds in weight to a maximum of 0 7 gm for individuals weighing more than 130 pounds About 80 per cent of the patients had some type of yaws lesions before treatment while the remainder represented seropositive latent yaws of less than 5 years duration Originally 36 per cent of the group had infectious types of lesions either frank florid yaws or some other secondary type of eruption About 43 per cent of the cases had non infectious types of lesions including plantar and palmar hyperkeratosis late skin lesions bone involvement and juxta articular nodules

Rapid clinical improvement followed the first treatment in nearly all cases with lesions, and open, infectious types of papules usually were healed by the end of the first week In a few patients, in whom frequent dark field examinations were made on serum from lesions, it was found that treponemes disappeared in less than 24 hours in some while in others organisms could still be found for longer periods but seldom after the first few days following the first treatment By the end of the first year after treatment results were classed as unsatisfactory because of relapsing lesions in about 16 per cent Two and a half years after treatment the percentage with relapsing lesions had increased to about 32 per cent of 464 cases Among patients who were given 4 to 6 treatments unsatisfactory results occurred in about 18 per cent, and among those who had only one or two treatments, clinical treatment failures amounted to more than 3- per cent

The Kolmer-Wassermann reaction was used to follow serologic changes after treatment In a special group of cases in which quantitative tests were done it was found that the level of the reagin as high before treatment as would be expected in syphilis in comparable stages of the disease declined gradually after treatment over a period of 6 months or more in the majority The serological reaction had reverted to negative in about 33 per cent of 1 265 patients during the first 6 months following treatment, in about 40 per cent of 1,112 cases during the first year and in about 50 per cent of 414 cases followed as long as two and a half years Again the number of treatments apparently had an appreciable effect on the proportion of cases showing sero-reversal which at 18 months after treatment amounted to only about 11 per cent of those given only one treatment, 59 per cent of those given 4 treatments and 65 per cent of those given 6 treatments

The bismuth salicylate used was prepared in the laboratories of the Jamaica Yaws Commission This was a 10 per cent suspension in olive oil of bismuth salicylate containing about 57 per cent of bismuth Injections were given into the gluteal muscles the dosage being graded according to body weight Infants weighing 10 pounds or less were given 0 2 c c of the suspension and the amount was increased by 0 2 c c for each additional 10 pounds of body weight to a total of 3 0 c c for patients weighing 140 pounds or more The clinical diagnoses in the group of patients treated with bismuth were comparable to the group given neoarsphenamine 35 per cent had infectious types of lesions 4- per cent had other types of lesions and 23 per cent had sero positive latent yaws of less than 5 years duration

In general the clinical and serologic response to bismuth therapy compared favorably with that following treatment with neoarsphenamine Lesions healed somewhat more slowly following bismuth administration, and dark field examinations frequently revealed the persistence of spirochetes in infectious lesions for several days after the first treatment After 1 months observation the clinical relapse rate was about 14 per cent of 948 cases and this increased to about 30 per cent of 215 cases followed as long as two and a half years Following bismuth therapy relapse rates were greater when fewer than 4 injections were given and less when 4 to 6 treatments were given The slight difference in relapse rates between the groups given neoarsphenamine or bismuth salicylate are not significant

Quantitative Kolmer Wassermann reactions revealed a gradual decrease in reagin titer after treatment with bismuth similar to that following neoarsphenamine Positive tests had become negative in 46 per cent of 535 cases after 6 months in 46 per cent of about 500 cases at the end of a year and in about 60 per cent of 119 cases after two and a half years When the number of treatments was taken into consideration it was found that the proportion of cases showing serologic reversal increased with the number of treatments. At 18 months after treatment only about 12 per cent of cases given one injection had negative serologic reactions this increased to about 58 per cent following 4 injections and to 62 per cent following 6 injections

Apparently results were slightly in favor of bismuth salicylate when compared with neoarsphenamine in the treatment of yaws but observed differences were too small to be statistically significant Furthermore Turner s observations although based on a much smaller group of cases were quite different He found that during a year after treatment with 6 weekly doses of neoarsphenamine about 10 per cent of 104 yaws cases showed relapsing lesions while complement fixation reactions had become negative in 58 per cent A year after treatment with 6 weekly doses of bismuth salicylate results were classified as unsatisfactory because of relapsing lesion in 30 per cent of 13. cases while complement fixation reactions had become negative in only about 37 per cent [81] It is difficult to compare results of treatment in the series of cases described because there are so many variables including duration of disease before treatment the number and regularity of treatments and the climatic environment after treatment However it is probable that clinical and serologic cure of about two thirds of yaws cases may

be achieved by treatment with 4 to 6 injections of either neoarsphenamine or bismuth salicylate given at weekly intervals

Soon after the first reported use of penicillin in the treatment of syphilis by Mahoney Arnold and Harris in 1943[161] reports began to appear on the successful use of this antibiotic in yaws Gordon treated 50 cases of yaws with early or late types of lesions with a total 1 2 million units given in divided doses every 3 hours for 8 days for cases with early lesions and with a total of 3 4 million units given in divided doses every 3 hours for 21 days for cases with late lesions Clinical improvement was prompt spirochetes disappearing from lesions in 8 to 24 hours after the first treatment Skin lesions healed rapidly, and there was a marked decrease in titer of the Kahn test during a two-month observation period[16] Tompsett and Kauer, who treated 5 patients with early secondary yaws lesions with 20-25 000 units of penicillin every 4 hours to a total of 250 000 units in one case and 400 000 units in the others, reported that the lesions healed in a few days, becoming darkfield negative in 24 hours or less Serologic tests remained positive during the few weeks observation period[163] Nery Guimaraes treated secondary yaws cases with small doses of penicillin to determine the minimal amount needed to produce clinical cure He found that as little as 100 to 150 units given every 4 hours to a total dosage of 10 000 to 15,000 units produced clinical cure in 17 days but that 50 units given every 4 hours to a total of 12 000 units in 40 days failed to produce cure When he gave 400 units 3 times a day until 17,000 to 19 000 units were given or 1 600 to 3 200 units once a day until 48,000 to 64 000 units were given, clinical cures resulted[161] Dwinelle and associates described the results of penicillin treatment of 500 cases of primary and secondary yaws in Haiti[16] Follow-up observations were made for periods as long as 12 months after treatment in the majority Patients were treated by one of three schedules 200 cases were given 40 000 units of aqueous penicillin every 3 hours for a total of 1 2 million units in 4 days, 151 patients were given penicillin calcium in peanut oil and beeswax once a day for 2 days for a total of 600 000 units, 900 000 units or 1 2 million units depending upon the patients' ages, and 149 patients were given the same total amount of the penicillin-oil-beeswax preparation in one day in divided doses given 12 hours apart Clinical improvement in patients on the first treatment schedule was rapid and remarkable lesions becoming dark field negative in 8 to 12 hours and healing in a few days Severe toxic reactions were not encountered although about one half of the patients had febrile Herxheimer reactions

with temperature elevations to 100–104°F 4 to 8 hours after the first treatment, and about one fifth of them showed brief secondary temperature elevations from the third to fifth days Since the patients in the other two groups were treated on an ambulatory basis it was not possible to follow their immediate clinical course although when seen 3 months after treatment they showed complete healing of all lesions in most instances During the 12 month follow up period apparent cure as indicated by continued absence of clinical activity and negative Kahn reactions was attained in nearly 27 per cent of the group treated over a 4 day period in 11 per cent of those treated for 2 days and in about 6 per cent of those treated in one day Satisfactory progress as indicated by freedom from lesions and a progressive reduction of the Kahn titer to a low level was noted in an additional 63 per cent of the first group 82 per cent of the second group and 86 per cent of the third group, so that clinical cures resulted in from 90 to 93 per cent of all cases Unsatisfactory progress including clinical relapses serologic relapses or re infections were noted in about 10 per cent of the first group and in 7 per cent of the other two groups Serologic relapses accounted for the majority of unsatisfactory results[165 166] The clinical results of treatment with penicillin as used by Dwinelle and his coworkers appear to be better than those following therapy with 4 weekly treatments with neoarsphenamine or bismuth salicylate after which unsatisfactory clinical progress including only clinical relapses was noted in about 15 per cent

It is of interest to compare Dwinelle's results with those following the treatment of syphilis with penicillin When cases of primary or secondary syphilis were treated with a total of 1 2 million units of amorphous penicillin given in divided doses every 3 hours for 4 or 7 5 days the total cumulative clinical failure rate (not including serologic relapses) for the first 12 months was nearly 15 per cent of more than 900 patients on the shorter treatment schedule and about 10 per cent of more than 600 patients on the 7 5 day schedule[167] In Dwinelle's series of early yaws cases treated with 1 2 million units of penicillin the total failure rate including serologic relapses for the first year was about 10 per cent for the four day schedule with aqueous penicillin and about 7 per cent for the other schedules using penicillin in oil and beeswax The results appear to be better in yaws than in syphilis as far as clinical relapses are concerned but the observation period was less than 12 months in a number of the yaws cases while the results in syphilis cases were based on the complete 12 months If all yaws cases

had been observed the full year, more clinical failures might have occurred On the other hand, penicillin treatment appears to be followed by a greater proportion of serologic reversals in early syphilis than in early yaws In a series of cases of secondary syphilis treated with 1 7 million units of aqueous penicillin, 20,000 units every 2 hours for 7 days 64 per cent had attained sero-negativity by 12 to 15 months following treatment[1 8] while in Dwinelle's series of yaws cases, treated with somewhat smaller total amounts of penicillin during a shorter treatment period 1 to 4 days only about 17 per cent had attained sero-negativity during observation periods up to one year However, there was a progressive reduction in Kahn titer to a low level in the yaws cases, and more of them would have attained sero negativity had the observation period been longer Again it is difficult to draw conclusions from any observed differences because of such variables as type of penicillin the treatment schedule, the criteria for unsatisfactory results and the sensitivity of serologic tests employed It is probable that on strictly comparable treatment regimens the response of yaws and syphilis to penicillin therapy will differ little if at all It seems certain that penicillin is the drug of choice in the treatment of yaws

In the evaluation of the effect of any form of treatment of treponematous disease one must not fail to take into consideration the natural evolution of the disease without treatment Yaws and syphilis both tend to early latency with spontaneous healing of lesions and in both serologic tests gradually decrease in titer and become spontaneously negative in a proportion of cases after a period of years However complete recovery during the first year or two of the disease probably occurs rarely, if at all, without specific treatment so that cures following treatment early in the course of the disease must be ascribed to the treatment From an analysis of available material on the therapy of yaws it may be concluded that the administration to cases of primary and secondary yaws of 4 to 6 injections of neoarsphenamine or bismuth salicylate at approximately weekly intervals will be followed by clinical failures (relapses) in about 15 per cent during the first year, that the remainder will show satisfactory progress with absence of lesions and declining titer of serologic tests and that sero negativity will be attained in 40 to 50 per cent of cases Administration of 1 2 million units of penicillin over periods of from 1 to 4 days apparently is followed by fewer unsatisfactory clinical results and although the proportion of cases becoming completely sero-negative appears to be smaller serologic titers

decline to a low level and with longer observation periods tests probably will become negative

With the development of new penicillin preparations which delay absorption and prolong effective blood levels such as procaine penicillin with aluminum monostearate in oil it is possible that one injection of 1 million units will cure the majority of cases of either early yaws or syphilis Wright and associates state that effective penicillin blood levels are necessary for at least 7 hours to insure the maximum cure rate in early syphilis and that the majority of cases of early syphilis probably can be cured by one injection of a suitable preparation of penicillin[169] It is probable that yaws will respond in the same way

In general it may be said that late lesions of yaws, including ulcerative and destructive lesions of the skin and of the bones respond to the same therapeutic agents that are effective in early yaws but clinical and serologic improvement is slower Large ulcers may require various forms of local therapy including skin grafts to bring about healing Long standing bone deformities resulting from proliferation of new bone are affected little by specific therapy Juxta articular nodules and tenosynovitis commonly become smaller following treatment and may disappear entirely

Control Measures

It is to be emphasized again that yaws is a major world problem Not only does the disease constitute a vast tropical reservoir of treponematosis from which spread to other parts of the world may occur but it is also the cause of great suffering and disability with resulting economic loss The disease can be controlled and with continuing efforts of trained personnel eradication from many areas might be accomplished

Control of yaws conceivably might be achieved in three ways 1) the population might be immunized) transmission of the infectious agent might be interrupted and 3) sources of infection might be eliminated by treatment of the disease[81] Treatment of yaws is the only practical method available at the present time because immunization is impossible due to the lack of a suitable antigen and interruption of transmission through such methods as isolation of patients with infectious lesions is entirely impractical Control through treatment must depend upon the rapid elimination of infectious or potentially infectious yaws cases This includes those with lesions of the secondary type in

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arsphenamine was given to some patients in bismuth treated areas and likewise bismuth was used occasionally in neoarsphenamine treated areas A large proportion of persons designated for treatment received the scheduled number of injections

Because relapsing lesions occur in perhaps 10 to 15 per cent of cases of early yaws following 4 to 6 injections of the preparations used each area was visited again at intervals of 4 to 8 months in order to treat persons with relapsing lesions or those with new infections To locate these cases a rapid resurvey was made by yaws inspectors a few weeks in advance of the scheduled re treatment period As a result of this method of preliminary survey treatment resurvey and re treatment the number of cases of manifest yaws found at the original survey and treatment period was quickly reduced by about 80 per cent and maintained at a low level during 3 years of follow up activities Furthermore primary attack rates the number of new infections with yaws detected each year per thousand of the population without previous yaws were reduced by 80 to 90 per cent during the period of control activities as compared with the year before the initial treatment period Results were slightly better in areas where neoarsphenamine was used but very satisfactory results followed the use of bismuth salicylate and the cheapness ease of administration and relative freedom from toxic reactions favor bismuth rather than neoarsphenamine for the control of yaws by mass treatment reserving the arsenical preparations for cases responding slowly to bismuth In one year a single treatment unit covered 3 new areas with a total population of about 10 000 people and re surveyed and re treated 9 additional areas with a total population of about 4 000 people Yaws prevalence varied from about 40 to 50 per cent It was found necessary to treat about 60 per cent of those with yaws or 25 to 30 per cent of the entire population at the initial treatment periods but during follow up periods treatment was given to only about 4 per cent of the total population group[60]

In most regions where yaws prevails the populations are primitive in their culture habits and hygiene and are scattered widely over areas which frequently are inaccessible Because transport and communication facilities are inadequate or non existent it is often difficult to entice patients into clinics for the first or for repeated treatments especially when only a single injection usually causes at least a temporary healing of lesions In controlling yaws through treatment the great need has been for a preparation which would be effective when given as a single treatment either intramuscularly or by mouth Unfortunately several

which treponemes usually abound and also patients with latent yaws of short duration It is known that the great majority of persons with infectious types of lesions have had yaws less than 5 years most of them less than 2 years and that the majority are children or young adults For practical purposes this narrows the field to persons in the younger age groups and to those who have either infectious lesions or early latent yaws Among more than 6 000 yaws cases seen in Jamaica 60 per cent of those with yaws of less than 5 years duration had lesions of the disease more than half of which were infectious in type The proportion of cases with active lesions diminished rapidly as the duration of infection increased but even after 20 years more than 2 per cent were found to have some type of infectious lesion[97]

Control of the disease with an impressive decline in the number of new cases was accomplished in Jamaica through treatment[110] Mobile treatment units covered successively adjacent areas in territory where yaws was prevalent Each treatment unit consisted of a physician a dispenser, a clerk and four yaws inspectors A preliminary survey of the entire population of each area by a trained yaws inspector served to locate essentially all persons with yaws lesions or with a history of having suffered from the disease during the previous 5 years A treatment team then entered each area and all persons with yaws lesions of any type and with sero positive latent yaws of less than 5 years duration were scheduled for treatment Because serologic tests are positive in more than 90 per cent of all persons who have had yaws less than 5 years and in only a slightly smaller proportion of those with early latent yaws who have had little or no treatment for control purposes serologic tests to eliminate the few sero negative cases from treatment probably is not necessary or practical For the sake of humanity and good public relations as well as for control purposes it was decided to treat all persons with yaws lesions of any type and not to restrict treatment to those with lesions of the infectious type Since the objective was community control of infection and not necessarily biologic cure of the individual treatment schedules were aimed at rapid healing of lesions and a minimum of relapses Previous studies had indicated that as the number of treatments with an arsenical or bismuth preparation was increased from 1 to 4 the number of subsequent relapses decreased considerably but that increasing the number of treatments beyond 4 caused very little additional decrease in relapses Therefore a schedule of 4 to 6 weekly injections was decided upon In some areas neoarsphenamine and in others bismuth salicylate was used almost exclusively, although neo-

where conditions are favorable for its transmission and development These conditions include adequate moisture and warmth an abundant vegetation and a population of primitive culture and insanitary habits Yaws is commonly a community disease and most of the inhabitants are infected at some time Infection occurs most frequently in child hood but the disease may be acquired for the first time in adult life Infection with *T pertenue* stimulates an immune response on the part of the host which provides a serviceable resistance to reinfection with the same or other species of treponemes The disease proceeds through a regular pattern of evolution which is characterized by a single primary lesion by a generalized granulomatous secondary eruption and after a period of latency by late lesions of the skin and bones both hyper trophic and destructive It is probable that on rare occasions cardio-vascular and neural structures are invaded with the production of symp tomatic lesions The causal organism *T pertenue*, is found in large numbers in primary and secondary lesions, but spirochetes are scarce in late lesions Serologic tests for syphilis are strongly positive in nearly all cases with active lesions of yaws The disease responds readily to the same therapeutic agents which are effective in syphilis Bismuth the various arsenicals and penicillin have been employed with success Community control of yaws must depend principally upon the elimi nation and control of infectious cases by means of treatment Public health education and isolation are other factors which must be consid ered in control

injections of the arsenical bismuth preparations are required to insure a reasonable chance of cure, and none of the preparations recommended for the oral treatment of yaws has proven effective, but there is great promise that some of the newer forms of penicillin will provide the ideal drug for a one treatment cure of yaws and it is probable that a single injection of 1 2 million units of a preparation which provides prolonged blood levels will cure the majority of cases of yaws and prevent relapses in a large part of the remainder Penicillin is easily administered, serious toxic reactions are extremely rare, the antibiotic is stable at ordinary temperatures in oil vehicles, and the cost for a single curative dose is less than that for a series of several doses of the less effective arsenicals and not much more than the cost of several doses of a bismuth preparation Moreover, the great saving of time of both professional personnel and patients which could be effected by a single dose treatment of yaws, would greatly lower the costs of control campaigns After preliminary survey an area which would require a month or two for the treatment of all yaws cases with former methods, could be covered in a week or less, if the one injection treatment with penicillin were used

In addition to treatment other means of control should be attempted including public education about the disease Among some groups yaws is thought to be a "God sick ness' and therefore, inevitable The people should be informed through talks by yaws inspectors and others and through pamphlets and posters where practical that yaws is transmitted from the sick to the well, and that separation of the two groups will prevent spread of the disease It should be emphasized that infection usually occurs through a cut scratch abrasion or ulcer and that these should be given care and kept covered The possibility of relapse and of reinfections and the need for adequate treatment should be stressed However circumstances for the control of yaws are seldom ideal Superstition taboos indolence and stupidity in addition to difficulties of travel and communication frequently constitute almost insuperable obstacles to control efforts

Summary

Yaws is a chronic relapsing infectious disease caused by *Treponema pertenue* Its origins are unknown but it is a very ancient disease which is closely related to other patterns of treponematosis including syphilis bejel and pinta It is a disease which is widespread in the tropical world

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CHAPTER XXIX-A

GOUNDOU

By MAJOR JAMES STEVENS SIMMONS Medical Corps U S Army

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Definition — Goundou or big nose is a chronic condition observed in Africa South America and elsewhere which usually is characterized by the slow development of symmetrical oval tumors on both sides of the nose due to hypertrophy of the nasal bones and the nasal processes of the superior maxilla The peculiar appearance which results from this permanent paranasal deformity led MacAlister (188) to refer to persons affected with goundou as the horned men of Africa The disease has been reported from locations in which yaws is endemic and there is some evidence which suggests that goundou may be due to this infection

Synonyms — Goundou is also known as henpuye or dog nose (Gold Coast) anakhre or gros nez (French Ivory Coast) and uyulue (Bantu name)

History and Distribution

Since 1882 when MacAlister described the horned men of Africa goundou has been reported from many parts of the world It is not uncommon in West Africa especially in the region of the Gold Coast and the Ivory Coast It is less common but is widely distributed in Central and East Africa the West Indies South America China Sumatra the Philippines Polynesia and in other tropical localities The disease has been seen only rarely in white men and is more prevalent among dark skinned races A condition resembling goundou has been observed among certain of the higher apes especially chimpanzees

168 PROGRESS REPORT Rapid Treatment of Early Syphilis Co operating Rapid Treatment Facilities and U S Public Health Serv ice Division of Venereal Disease progress report—December 1948
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March 1 1951

According to Botreau Roussel and Cornil (1924) the paranasal outgrowths of goundou are not true tumors but result from an inflammatory hyperplastic osteitis While the facial tumors are characteristic of goundou it is claimed that similar bony lesions may exist elsewhere in the body Botreau Roussel (1925) who believed goundou to be a manifestation of yaws observed that in tertiary yaws the exostoses were found in different locations as follows para nasal 121 other tumors of the superior maxilla 16 skull 2 tibia, 69 fibula, 5 femur 4 radius 5 and clavicle 3 However other observers have questioned the relationship between these diseases

TREATMENT AND PREVENTION

According to Botreau Roussel (1925) early cases of goundou improve after four or more injections of neosalvarsan However for the removal of the para nasal tumors surgical treatment is necessary After incision of the periosteum the bony outgrowth is cut out with a chisel

As the cause of goundou is not yet definitely determined it is futile to at tempt to formulate rules for the prevention of this disease

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July 1 1933

Etiology

There has been some speculation and controversy as to the cause of goundou Some observers believe it to be a specific disease others have suggested that it may be caused by the presence of insect larvae in the nostrils that the tumors are malformations due to non union of the nasal and frontal bones, or that they are an example of atavism referable to some tribal peculiarity of the original negro stock Still others have suggested that the condition may be due to syphilis At present certain observers (Botreau Roussel, 1925, Botreau Roussel and Cornil 1924) believe that goundou is a hypertrophic osteitis caused by yaws In support of this theory it is stated that goundou occurs in locations where yaws is common that it frequently follows closely after secondary yaws, often in young children that it is usually accompanied by other signs of tertiary yaws which can be controlled by arsphenamin during the early stages, and that goundou patients are immune to inoculations with Treponema pertenue According to Manson Bahr (1931) spirochetes have been demonstrated recently in sections of the bony tumors of goundou However as many others including Roy (1925), Pasqual (1928) Carroll (1927) and Aranjo (1928) do not consider goundou to be a manifestation of yaws it may be stated that the cause of goundou still is undetermined

Symptoms and Pathology

Goundou usually appears during childhood It begins gradually, and the patient soon develops a severe and persistent headache and in some cases, pain in the nose In a short time there is a thin purulent nasal discharge which may be tinged with blood, and a small swelling the size of a bean soon appears on each side of the nose Some of the patients complain of osteocopic pains at night While the swelling usually is bilateral it may be limited to one side It affects the nasal process of the superior maxilla but does not involve either the cartilage or the skin There may be polypoid excrescences protruding from the nasal mucous membrane In goundou there usually is a generalized enlargement of the lymphatic glands

After six or more months the headache and the nasal discharge subside but the bony tumors continue their slow but regular growth and in some cases may become as large as the fist As a rule they are oval with the long axes inclined downward from within outward During its development the tumor may involve other bones of the face causing an inward bulging of the nostrils and obstruction of the nasal passages In some cases the hard palate may be affected resulting in marked deformity The orbit is not invaded but the tumors may become so large as to obstruct the line of vision

CHAPTER XXIX-B

LYMPHOGRANULOMA VENEREUM

By GEORGE A HARROP

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Definition —Lymphogranuloma venereum is an infectious disease caused by a specific filterable microbiotic agent which is ordinarily transmitted by means of venereal contact It is essentially chronic in character and a fatal termination unless due to a complication is very rare A complete subsidence and permanent disappearance of all clinical signs and symptoms are very frequent even without treatment

Introduction

Lack of a clear comprehension of the common etiological basis of the several forms of this disease during the course of the last hundred years has given rise to a rather extensive and confusing nomenclature based on its various clinical manifestations These names are chiefly anatomical or descriptive in character The following are frequently found in the literature lymphogranuloma inguinale or poradenitis venereal lymphogranuloma lymphopathia venereum lupus vulvae

Incidence and Distribution

Accurate data on the extent and distribution of lymphogranuloma venereum are completely lacking Suffice it to say however that it is now definitely established that it is not primarily a disease of the tropics as was supposed formerly The incidence in the temperate zone is considerable and seems to be increasing at a rather disconcerting rate This increase may be more apparent than real and possibly is due to the recent increase in clinical interest and improved methods of diagnosis The disease is particularly frequent among the sexually promiscuous and among those addicted to improper sex practices It is common in the lower economic strata of the population especially among the negroes and hence particularly in the South It is also prone to appear in seaports in localities frequented by sailors It is clear that the disease has a natural tendency to spontaneous cure and that the long standing ulcerative cases probably are those which are exceptionally persistent The experience of the Venereal Disease Clinic of the United States Public Health Service at Hot Springs Arkansas[6] probably represents a fair sampling of the disease since patients there come from all parts of the country although more particularly from the surrounding territory In 3 000 venereal admissions in 1937-39 there were 1 6 per cent of cases of active lymphogranuloma venereum disease Other clinics show a higher incidence always greater in the colored race Such for example is the series recently reported from San Francisco[1] and that from St Louis[9] It is commonest in adult life up to the age of 40 In New York City the anorectal and genital types of lesions are much more common than buboes[7] The reverse appears to be the case in the Southern colored patients The probability, which has been strengthened recently by newer diagnostic techniques that a large group of latent infections exists especially among the sexually promiscuous, is discussed below in the section on diagnosis

Etiology

Lymphogranuloma venereum is caused by a filterable agent belonging to a group which includes psittacosis trachoma inclusion blennorrhea and some of the viruses causing atypical pneumonia This group is distinguished from other viruses by reason of certain similar and apparently unique characteristics The agent producing lymphogranuloma venereum in common with that of psittacosis and that of trachoma has been shown to have a definite cycle of morphological development[23] passing through the stages of free elementary bodies initial bodies and finally of plaques containing elementary bodies which presumably break up and extrude their contents The etiological agents of all three diseases are similar in morphology tinctorial characteristics and size The plaques of the

chronic elephantiasis with vulval ulceration, climatic bubo, strumous or scrofulous bubo esthiomene and inflammatory stricture of the rectum The terms Nicolas Favre disease and fourth venereal disease have been used also Lymphogranuloma venereum is to be sharply differentiated from the other venereal diseases, and especially from granuloma inguinale, a disease caused by Donovan s bodies and characterized by chronic ulcerations and from chancroidal infection or ulcus molle due to *Hemophilus ducreyi* a gram negative bacillus These latter diseases of course demand other methods of diagnosis and treatment as discussed in other chapters in Oxford Medicine

Within the last decade the firm establishment of a single etiological agent has synthesized the previously poorly understood group of pathological disorders now recognized as typical manifestations of lymphogranuloma venereum into one disease entity Before that advance was made the following clinical syndromes were considered as separate maladies (1) Climatic bubo was observed characteristically in the tropics particularly by naval surgeons and rather vaguely ascribed to the climatic conditions which pertain there This climatic bubo is recognized now as being identical with strumous or scrofulous bubo It occurs more frequently in the male and particularly among negroes It has long been known to venereologists of the temperate zone and in the past usually has been attributed by them to chancroid or tuberculosis (2) Esthiomene from the Greek meaning eating or eroding embraces a syndrome combining chronic ulceration with coincident or subsequent elephantiasis of the vulva which often spreads and ultimately involves the other external genitalia and the anorectal tissues Huguier s description of this condition has become classic and is quoted frequently [1] He said this chronic malady is characterized by a leaden or violaceous tint of the parts Deformity ulceration and destruction may occur with concomitant hypertrophy and infiltration of such a nature that the orifices and canals which open into the vulvoanal region can be at the same time ulcerated enlarged and strictured Often it was confused in the last century with cancer syphilis and tuberculosis Fournier emphasized this syndrome in 1875, believing it a manifestation of syphilis and for many years it was known as the anorectal syphiloma of Fournier although it was recognized early that treatment with the usual antisyphilitic remedies was ineffective (3) Inflammatory rectal stricture found commonly in the female and previously thought to be associated chiefly with tuberculosis, neoplasm or another venereal disease now is recognized as due in many instances to lymphogranuloma venereum Some authors believe that it is responsible for one third or more of all rectal strictures As Frei[5] states esthiomene and rectal stricture always have occurred frequently in the same patients but the gynecologists usually have noticed only the esthiomene and the surgeons only the rectal stricture

Incidence and Distribution

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lymphogranuloma venereum virus reach a diameter of 3 5 to 5 micra or even 7 micra The elementary bodies have an average diameter of 400 millimicra The initial virus bodies as seen in the yolk cells, according to Rake's measurements have a diameter of about 1 micron or more than twice that of the original virus particles Compared to other filterable agents or viruses that of lymphogranuloma venereum is relatively stable and resistant to chemical and physical agents

Of the so called virus diseases so far examined only four, trachoma inclusion blennorrhea a pneumonitis of mice (Nigg [1]) and lymphogranuloma venereum are definitely known to respond to chemotherapy with those sulfonamide drugs so far developed Psittacosis and pneumonitis (Eaton) do not so respond A close antigenic relationship exists between lymphogranuloma venereum and psittacosis and a definite relationship exists between these and the agents of trachoma and inclusion conjunctivitis as well as meningopneumonitis (Francis and McGill[1])

The virus of lymphogranuloma venereum has been transmitted to monkeys, mice guinea pigs cats dogs and to other animals Its pathogenicity is low, and little increase in virulence follows successive passage It is possible to transmit the agent to chick embryos but not to hatched chicks a point of distinction from the agent of psittacosis which otherwise has so many similarities Lymphogranuloma venereum produces no characteristic pathological tissue changes other than the virus bodies which may be detected microscopically with appropriate stains in suitable preparations

Clinical Description

Lymphogranuloma venereum is transmitted in most cases by means of venereal exposure to infected individuals It is spread also in a variety of other ways involving introduction of the infecting agent through the intact or injured skin mucous membranes conjunctivae or even by inhalation of the sprayed virus, during experimental procedures into the respiratory tract Such accidents have happened rather frequently They have been due to chance cuts or abrasions on the hands of surgeons, suffered during the excision of buboes or other operative procedures to children sleeping with infected adults suffering from open lesions[19, 7], to the use of infected instruments such as enema tubes and to the accidental laboratory infection of persons working with the virus[1, 13]

The clinical evidences of the disease usually appear after an incubation of 5 to 25 days but occasionally only after a period of several weeks or months In instances of laboratory infection known to the author the first manifestations have appeared within twenty four hours of an accidental subcutaneous inocula

tion of virus by means of the needle of a hypodermic syringe filled with infected material Generalized symptoms often are noted at the onset of this infection particularly the inguinal variety but by no means are observed invariably This has been true also in the group of laboratory infections observed by the writer and his associates[1] The size of the infecting dose and the portal of entry would appear to be the most important determining factors Questioning may recall to mind a mild or more severe indi position frequently considered to have been flu or a nondescript infection Headaches fever sweats chills weakness, muscular soreness and tenderness joint symptoms rheumatic pain either passive or on movement with or without heat or swelling and sore throat are common symptoms Rashes and conjunctivitis occur It would appear however that in the majority of cases acquired by venereal exposure the clinical disease is local or limited in nature without a phase of acute obvious systemic invasion The latter probably occurs as already stated where a massive infecting dose of the agent is sustained or where the virus is widely diffused from the portal of entry For this reason perhaps antibodies appear to be built up rather slowly in most of the venereally acquired cases *This contrasts with known instances in our series* where an accidental infection probably more massive in character was followed rapidly by positive skin or complement fixation reactions An increased sedimentation rate and a moderate leucocytosis occur and sometimes (Frei) a transitory positive Wassermann reaction is obtained Secondary anemia is frequent in the active forms of the disease Gutman[1] has reported the common occurrence of hyperproteinemia due to a large increase in serum globulin in the various stages of lymphogranuloma venereum It is not necessarily related to the *activity of the lesions It is particularly marked in persons with chronic com*plications such as rectal stricture It also occurs in association with buboes and where present is suggestive and of diagnostic help particularly before the Frei reaction becomes positi e It is remarkable that this protein change persists for many years and may be permanent Recent evidence relates it to the complement fixing antibodies

It may be assumed for descriptive purposes that the first evidence of the disease as commonly acquired by sexual intercourse is the appearance of the pri*mary or initial lesion the so called lymphogranulomatous chancre at the portal* of entry generally on the genitalia This frequently goes unobserved by the patient often is not discovered at all or may be demonstrated only by the physician when he is consulted on account of other manifestations of the disease This initial lesion usually is described as a small herpetiform vesicle or ulcer with clean edges and a whitish gray base circular or lenticular in shape sometimes multiple usually inconspicuous and in most cases no bigger than a pin s head Usually it is painless but when observed patients often complain of

burning and irritation from it There is seldom infiltration or true induration In the male it may be found on any part of the glans penis or inner surface of the prepuce It is seen more rarely in the female where it may occur on any part of the vulva commonly at the fourchette Certain other primary lesions are described as papules or as small firm elastic nodules Confusion with the syphilitic chancre is possible and in the past probably not uncommon More frequently the patient appears for medical help because of disabilities due to one or more of the varieties of lesion which ordinarily characterize the disease

Inguinal Type Climatic Bubo, Venereal Lymphogranuloma

This type is characterized by involvement of the regional lymph nodes, producing first a stiffness or aching in the groin on walking followed by palpable and visible enlargement of the nodes In most cases at first these are discrete and easily movable The swelling then may regress but more frequently in untreated cases the lymph nodes gradually become adherent and form a single, fluctuant inflammatory mass which if untreated, finally breaks through the overlying skin, forming chronic draining sinuses with multiple foci of suppuration From 40 to 60 per cent of the nodes suppurate The pus usually is thick, grayish and filled with necrotic material when collected aseptically and inactivated, it is the source of material for the Frei skin test The clinical appearance of the inflammatory mass is similar to that found in tuberculosis of the lymph nodes The inguinal type of lymphogranuloma is most common in the male, and it is probable that this is due to the anatomical difference in the lymphatic drainage of the region in the two sexes The adenitis is unilateral in perhaps three fifths to four fifths of the cases Following the infecting venereal exposure the swelling of the lymphatic nodes appears after a variable time, from one to several weeks and the observation of a preceding primary lesion is made in only a small proportion of patients In females the bubo process may develop unnoticed inside the pelvic girdle in the perianal or deep pelvic lymph nodes only where the initial lesion is in the urethra or on the clitoris or on the anterior part of the vulva, according to Stannus will the inguinal lymph nodes ordinarily become infected

Involvement of the regional lymph nodes is observed in cases of laboratory infection where the agent gains entrance through the skin of the hand or arm In one case in our series where infection presumably occurred by inhalation of the agent during laboratory manipulation intranasal inoculation of mice enlargement of a supraclavicular lymph node and of nodes in the anterior cervical chain was observed Enlargement of the spleen has been recorded but significant clinical splenomegaly cannot be common

Ulcerative Chronic Elephantiasis of the Genital Anal and Rectal Regions

Ulcerative chronic elephantiasis of the genital anal and rectal regions esthiomene a disease more common in women usually commences with ill characterized ulcerations or mild diffuse inflammation of the vulva anus or rectum These lesions persist become aggravated subside reappear and if neglected eventually may distort or destroy the entire genitoanal area Perirectal abscesses appear and fistulae are fairly common around the anus and buttocks The entire progression of this disease is a matter of months and years and various grades of structural changes may be produced

The elephantiasis has been attributed to hypertrophy produced as a consequence of impaired drainage and resulting stasis and to edema due to disease or excision of the regional lymphatic nodes It has been asserted also that the process is primarily inflammatory in nature a retrograde thrombotic lymphangitis originating in the lymph nodes When chronic in character such an inflammatory reaction in the subcutaneous and submucous tissues might well lead to lymphatic obstruction induration and fibrosis

Recent studies indicate that both stasis and inflammation may be involved in the lesion in varying degrees This has been indicated recently by the results of treatment of this condition which until the introduction of the sulfonamides was generally quite disappointing Kampmeier and Larsen[1] recognize two types one due to local lymphatic obstruction resulting from an exudative inflammatory reaction and the other due to lymphatic obstruction as a result of cicatricial contraction either locally or in the regional lymph nodes or both Excision of lymph nodes may contribute to this impairment of drainage and is an excellent argument for conservatism as regards surgical interference The rapid effectiveness of chemotherapy in certain cases indicates on the other hand that the elephantiasis may arise from an active inflammatory process Their successful results in two cases of nine and of seven years standing respectively indicate to these authors that the virus infection may be active for very long periods The type of pathological change provides an index of the probable result to be anticipated from chemotherapy Irrespective of duration if the picture is that of an active lymphangitis with little scar tissue the prognosis may be good If on the other hand the process has progressed to a dense sclerosive fibrosis of the subcutaneous connective tissue the results of chemotherapy cannot be satisfactory The prognosis of esthiomene always is doubtful the rectal type when untreated usually being less apt to become recessive than the genital type

The occurrence of malignancy in association with lymphogranuloma venereum of this chronic ulcerative elephantiasic type is not rare and an etiological relation has been suggested by a number of observers[1] Certain individual may pos

sess a susceptible epithelium that responds to such persistent irritating chronic inflammatory processes with cancerous changes These must be constantly borne in mind by the medical attendant

Anorectal Type of Lymphogranuloma Venereum Rectal Stricture

The essentially localized character of infection with lymphogranuloma venereum as usually observed is shown clearly in the anorectal type of the disease Rectal stricture is a common form of this malady and it may appear with slight or no preceding evidences of the disease It occurs characteristically 5 to 8 cm from the anus in a cylindric or annular form The constriction also may be tubular A proctitis usually is found when the stricture is discovered It is moderately severe often extreme and usually is ulcerative in character Because proctitis probably always precedes stricture diagnosis at this stage is of the greatest importance since prompt treatment then in the majority of cases results in complete and rapid cure Proctoscopic examination may reveal the lower bowel below and to a lesser extent above the constriction to be edematous ulcerated granular and friable Rectal stricture due to lymphogranuloma venereum even when relatively mild usually is characterized by the passage of blood and pus frequent and small bowel movements with varying degrees of tenesmus urgency to defecate and abdominal pain Great difficulty in defecation may develop later and marked constipation is found regularly with progressive narrowing of the rectal lumen Complete occlusion is uncommon but the lesion very frequently proceeds to a stage where ileostomy is required Perianal and perirectal abscesses and anal fissures and fistulae are complications often observed Ulcerative colitis as characteristically observed however is rarely due to lymphogranuloma venereum

The proximity of the rectum to the posterior vaginal wall in women and the direct lymphatic drainage of the cervix and vagina to the deep pelvic lymph nodes readily explain the mechanism of development of rectal disease In man on the contrary the lymphatics of the genital region drain mostly into the superficial inguinal lymph nodes A few lymphatics from the male genital structures do drain into the deep inguinal lymph nodes and thence into the iliac as well as into the deep pelvic nodes Therefore male cases of rectal involvement can be acquired as are the female cases by genital inoculation of the virus which migrates by way of the lymphatics toward the perirectum and rectum Frei states however that most rectal strictures in men are due to homosexual infection of the rectum Perverted sex practices doubtless account for lymphogranuloma of the lymph nodes draining the mucous membranes of the mouth tongue and pharynx Abortive and hidden forms especially in women may offer a dangerous

source of infection The possibility of accidental infection of the rectum by contaminated enema tubes is to be borne in mind in view of the relative hardiness of the lymphogranuloma virus and it emphasizes the importance of cleanliness and sterile precautions in hospital practice

Arthritis

Arthritis[7] develops in a considerable proportion of those who become chronic sufferers from this disease It varies in severity over a period of years and is seen most often in the smaller joints of the extremities Hydrops occurs with redness of the overlying skin and great tenderness Aspirated joint fluid does not contain the agent Joint destruction however is not found and full function is restored ultimately whenever the disease is cured or becomes completely quiescent

Differential Diagnosis

Cases of acute fulminating infection with the agent producing lymphogranuloma venereum may be confused with any acute febrile illness whose symptoms and signs may be similar or suggestive in character Because of its frequency the possibility of confusion with acute rheumatic disease acute respiratory diseases and acute enteric disorders should be especially emphasized A history of exposure and positive findings with the diagnostic aids to be mentioned below will serve to clarify the picture a matter of the greatest importance in view of the urgent indication for prompt treatment with the sulfonamides It is important to recognize that lymphogranuloma venereum can occur as an acute infection without apparent localization at least in the early stages and without tissue reaction at the point of invasion

A fully developed lymphogranuloma bubo in the inguinal region with characteristic signs and suggestive history is fairly conclusive but when the lesion is in an early stage or where typical signs and history are lackin other diseases must be considered such as chancroid syphilis Hodgkin s di ease lymphatic leukemia malignancy tuberculosis bacterial infection or even tularemia

Elephantiasis of the female genitalia anus and rectum with typical history is quite characteristic but if the picture is incomplete early abortive or otherwise unusual other possibilities such as granuloma inguinale filariasis chancroid syphilis neoplasm tuberculosis dysentery either bacillary or amoebic actinomycosis ulcerative colitis and others must be considered The various causes of proctitis must be considered where ymptoms and lesions occur at the lower end of the intestinal canal Mixed venereal infections are very common and often complicate the picture

Frei Test

This test depends upon the hypersensitivity of the skin in this disease to the intradermal infection of inactivated virus Such hypersensitivity usually continues throughout life probably because of persistent infection Some reversals have been reported including one in our series, in which case early and adequate chemotherapeutic treatment was employed before the infection could become established The material originally used by Frei consists of the diluted and sterilized pus of pure unruptured buboes This antigen is employed to induce a skin response in infected individuals One tenth c c is injected intracutaneously and the reaction is read at 48 or 72 hours When positive, an inflammatory slightly indurated papule develops which must be at least 0 5 cm in diameter Care must be taken to distinguish this papule from the more extensive erythema surrounding it According to Frei ' a positive reaction does not prove the disease still exists because reaction remains in healed cases for decades Anergy, transient or constant occurs The question of existence or non existence of the disease in such cases would appear to be a matter of definition The Frei test i claimed by its author to be positive in 95 per cent of buboes and 90 per cent of esthiomene In the hands of others it has not been found so specific but it has undoubtedly been the most important single advance in establishing and clearly defining the clinical picture of lymphogranuloma venereum The Frei reaction in the inguinal variety of the disease develops at about the same time as the enlargement of the nodes and in the anorectal type several weeks after appearance of the anal discharge Occasionally the test does not become positive until the nodes suppurate If the condition of anergy be excepted, most workers agree that a negative Frei test excludes present or past infection

The studies of Rake Shaffer and their associates [6] during the past four years have utilized the recent techniques for the cultivation and study of filterable agents and have shed new light on the problems of this disease and on the nature and properties of the causative agent They have succeeded in growing the agent originally obtained from bacteriologically sterile bubo pus on the chorio allantois of the developing chick embryo which appears to be selectively a particularly favorable soil and they have shown after repeated passages, that a highly effective antigen may be elaborated from this material which can be used for intradermal tests in a manner similar to that of the original Frei reaction The advantages which this water clear antigen possesses over that employed in the original Frei reaction consist of (a) its freedom from bacteriological contamination (b) the fact that the dosage may be precisely formulated in terms of the amount of infective material used and finally (c) its ready availability and reproducibility

Complement Fixation Test

Similar material lygranum may be used also as a basis for a complement fixation test, which seems to represent a lower threshold of immunological response than does the skin test so that in the course of the waxing or the waning of this response the complement fixation test may be positive in the absence of a positive Frei reaction. Practically all persons 98 per cent with clinical lymphogranuloma give positive fixation with this reaction when properly performed and 95 per cent of clinically normal persons fail to give fixation [6]. Nevertheless sera obtained from prostitutes or persons suffering from venereal diseases other than lymphogranuloma give positive fixation in a considerable proportion 68 per cent of cases. These findings confirm earlier observations previously received with considerable scepticism that a high percentage of positive Frei tests may occur in venereally exposed individuals. The evidence now points most strongly to the probability of the existence of a large group of latent and potentially dangerous infections with this virus in sexually promiscuous persons. Mention should be made however of the recently uncovered serological relationship of the virus of lymphogranuloma venereum with that of psittacosis and the viruses producing atypical pneumonia how much confusion this cross reaction may cause remains still to be investigated

Data on the rapidity with which the reaction with lygranum antigen as introduced by Rake employing the Frei technique or the complement fixation becomes positive is afforded by a group of laboratory infections in which the Frei reaction and complement fixation reactions were known to have been negative previously[1, 13]. In two of these instances the Frei reaction was found to be positive in 5 to 7 days after symptoms commenced and complement fixing antibodies appeared in the serum. Studies on this series as already stated also indicate the probability that with efficient early therapy the Frei reaction becomes weaker or even becomes negative with the amelioration of symptoms while coincidentally the complement fixing titer drops

One serious deficiency at this time is the lack of a reliable method of indicating whether the disease is in an active or quiescent phase and hence whether a given individual is probably infectious for others. The febrile or other generalized reaction which follows the intravenous injection of antigenic material whether derived direct from bubo pus from mouse brain passage material or from egg membranes has been suggested as a measure of this activity. Evidence is accumulating that this is not more reliable to demonstrate active disease. This procedure certainly has not been well established as a diagnostic aid and the intravenous injection of such material cannot be considered a routine matter or advisable except in the hands of specialists

The cross reaction complement fixation, which occurs with other virus infections as recently demonstrated , serves to complicate the study of the extent of latent lymphogranuloma venereum among the population That it is a much more widespread malady than had been suspected previously, however is now hardly open to question

TREATMENT

A large number of therapeutic agents have been employed in the past, including the usual antisyphilitic drugs salts of the heavy metals, iodine, antimony compounds such as tartar emetic and fuadin various topical applications to ulcerated areas radiation local rectal treatment including dilation and medicaments in the form of enemas and various supportive measures, including liver and iron for secondary anemias salicylates and heat for arthralgia, diet and rest

Surgical excision of buboes has been practiced extensively This has not been unattended with danger and probably is one cause for the production of elephantiasis due to obstructed lymphatic drainage Relief of rectal stricture by iliostomy frequently is required and should not be delayed unduly Instrumental dilation is not advised except in the hands of experts Palliative measures such as a low residue high vitamin diet oil retention enemas and rectal irrigations may be employed

The successful removal of rectal stricture by excision with end to end suture of rectal mucosa has been reported It is recommended that surgical treatment in this disease be limited to simple aspiration of buboes and to the relief of rectal strictures unless the situation is very exceptional

Of medicinal agents only two types require discussion at this time the use of antigenic material whether derived from human pus infected mouse brain material or egg membrane material for the general purpose of inducing a heightened antibody response and the use of the sulfonamides[15]

Sulfonamides — Of these the effect of the latter is clear cut and definite It appears that sulfathiazole and probably sulfadiazine are more effective than sulfanilamide which was used originally They should be used as early as possible and sufficient amounts should be employed in order to secure and maintain an effective blood level The importance of thorough treatment with the sulfonamides as early as possible during the acute phase is well illustrated by one of our own laboratory infections in which sulfathiazole was given on the fifth day of acute symptoms[13] Six grams were given daily for 3 days after which the dose was decreased and the drug was discontinued on the seventh day, when 7 grams had been given The temperature then was completely normal but a recurrence of the fever associated with sore throat and an edematous uvula occurred 12 days later and was treated with sulfanilamide and aspirin This febrile attack

lasted about 10 days after which there was another free interval of 10 days when a third bout of fever developed in which there was considerable pharyngitis, articular rheumatism and an enlarged supraclavicular node This attack lasted for 10 days and all symptoms subsided The patient then was given a rather intensive course with sulfathiazole, 1 5 gms three times daily a total of 100 grams Two other attacks of severe but localized cervical adenitis with slight fever occurred during the next 6 months following which he has been entirely free of further symptoms for the past 18 months Had really intensive treatment been carried out in the first instance it seems altogether probable that there would have been no recurrences

The use of sulfonamides which are poorly absorbed and may therefore be maintained in high concentration in the intestinal tract such as sulfasuccidine, has not yet been reported It does not seem likely that such a remedy used alone would be effective

The possibility of combining the use of antigenic material either simultaneously or in alternating courses with the sulfonamides also merits attention and is under study

The amount of sulfonamide treatment required varies with the type of lesion and its response to therapy It is probably best given in courses and with due reference to any coincident therapy with antisyphilitic agents which may necessarily be employed The complications of treatment with the sulfonamides in this disease do not present unusual features differing from those attendant upon their use in other conditions The not infrequent moderate secondary anemia observed in the untreated cases does not seem to be affected by sulfonamide therapy nor are idiosyncrasies to the sulfonamide drugs seen with greater frequency than in other conditions [3]

Antigenic Material — The intravenous or subcutaneous injection of Frei antigen has produced a favorable response in a small proportion of the cases reported but the results obtained by most observers have by no means been uniformly satisfactory

The most extensive recent report on this method of treatment is that of Kornblith [8] who employed 3 500 injections in 207 patients The results were particularly striking in the glandular (bubo) type of the disease symptomatic relief was afforded in the cases with rectal lesions The value of such treatment in the face of the results now obtained with the sulfonamides would seem to be questionable at this time and it does not seem indicated unless in exceptional circumstances where the sulfonamides have proven ineffective or for some reason are contraindicated

The tendency of this disease particularly the glandular type to heal spontaneously in a large proportion of cases 33 per cent of 300 recently reported by

Kornblith[19] must be carefully borne in mind in attempts to appraise the value of therapeutic procedures involving the intravenous or subcutaneous use of Frei antigen, particularly as derived from bubo pus

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CHAPTER XXIX-C

GRANULOMA INGUINALE

By FRANCIS M THURMON

Table of Contents

Synonyms —Ulcerating granuloma of the pudenda granuloma inguinale tropicum groin ulceration granuloma venereum serpiginous ulceration of the genitals and esthiomene form of granuloma inguinale

Definition — Granuloma inguinale is a specific infectious disease involving primarily the skin and mucous membranes seldom affecting the lymphatics and transmitted by direct contact The pudenda and contiguous surfaces are the commonest sites of involvement yet extragenital lesions do occur The entity is characterized by a gradual progressive superficial serpiginous recalcitrant type of granulation and ulceration with cicatrix formation of the invaded tissue The diagnosis is established by the demonstration of Donovan bodies obtained from the lesions

Introductory Note

Granuloma inguinale is an infectious disease which primarily involves the skin and mucous membranes Seldom is there associated lymphatic involvement In

addition to the clinical picture which is quite characteristic the diagnosis is established by the demonstration of Donovan bodies in deep tissue scrapings or by properly stained smears made from the base of biopsy specimens

Granuloma inguinale is transmitted by direct contact of an infectious medium with one which is not infected A break in the integument of the recipient during exposure is considered essential as a portal of entry before the infection can be established

The disease as seen in America, occurs chiefly in the negro race However, no race is immune Formerly regarded as a tropical disease it is now established that granuloma inguinale is not confined exclusively to the South but also has become increasingly prevalent and endemic in urban centres of the northern part of the United States

The lesions are characterized by gradual, progressive superficial serpiginous granulations ulcerations and cicatrices occurring usually in the genitocrural and genitoanal regions of both sexes Extragenital lesions are uncommon Ulceration is of rare occurrence in the early stages but frequently is present in the older and more advanced lesions The initial lesions of granuloma inguinale are elevated from the onset Multiple inoculation sites are not unusual The initial papules slowly develop into small rounded or button like masses and linear strands of bright red glistening verrucous granulations These fresh soft velvety vegetations are friable bleed easily and are only slightly sensitive to manipulation They are sharply defined against normal tissue By peripheral extension and autoinoculation the lesions slowly enlarge to form coalescent masses often involving the entire genital groin and perianal areas and even encroach on the adjacent surfaces of the abdominal wall and thighs The surrounding epidermis is thin and easily excoriated Seldom is there tendency toward spontaneous healing yet cicatrices are not infrequent At this advanced stage the affection is extremely recalcitrant and continues slowly to progress and may persist for months and even years Usually the general health is not seriously impaired An early diagnosis is desirable because response to therapy in the early phases is pronounced and decreases in direct ratio to the duration of the disease

History

Granuloma inguinale was first recognized in 1882 by McLeod[1] in Calcutta, India who called it serpiginous or lupoid ulceration of the genitals " Conyers and Daniels reporting from British Guiana in 1896 were the first satisfactorily to describe granuloma inguinale as a definite clinical entity Galloway[3] in 1897 reporting a case in London gave the first histological description and called the condition " ulcerating granuloma of the pudenda Donovan[4] in 1905 observed

"in scrapings from the deeper parts of these growths small forms oval in shape, about 1½ to 2 microns in length are found in the epithelial cells of the stratum malpighii or in macrophages usually in large numbers either scattered or in small round compact groups In subsequent literature these small forms are called Donovan bodies and are recognized as the essential laboratory findings necessary to establish the diagnosis The following year 1906 MacLennan[7] and Wise[8] reported the presence of spirochetes in the lesion and since that time numerous contributions have presented three views of the origin of the disease namely bacillary spirochetal and protozoal each view being in sharp conflict Modern investigators however consider the Donovan body to be the specific agent in granuloma inguinale It is a microorganism which probably belongs to the protozoan group although there is some evidence to suggest that it may be a fungus It is pathogenic for man and is transmitted only by direct contact There is dispute as to whether it ever has been cultured The incubation period is thought to be forty to sixty days

Grindon[9] reported the first cases of granuloma inguinale in the United States in 1913 and Symmers and Frost[9] 1920 are credited with being the first to recognize the Donovan bodies in cases seen in this country Goodman[10] 1920 writing an admirable paper presented 4 cases and described the disease as seen in Puerto Rico Randall Small and Belk[11] 1921, presented a short series of cases in Philadelphia where they believed the disease had existed for beyond fifty years Gage[1] writing in 19 3 presented 4 cases and stated a total of 59 up to that time had been reported in the United States and its dependencies Schochet[12] in 1924 tabulated 66 cases In 1926 Howard Fox[14] cited 15 ca es of his own and presented certain statistical data on 135 additional ones reported in the United States Fox emphasized that not only was the geographical distribution fairly generalized throughout the United States but also included India southern China Australia West Africa the East and West Indies and parts of Central North and South America Many cases have been reported from British Guiana and the Fiji Islands Since then a voluminous literature on granuloma inguinale has appeared in this country Cole[5] 1931 described the disease in Cleveland and stressed its endemic character in the North D Aunoy and von Haam[16] 1937 in an analysis of their 545 collected and personal cases concluded that the Donovan body is the specific etiological agent the infection being strictly a local one with no dissemination of the infectious agent and no toxic manifestations unless secondary infections occur They point out that secondary infections always must be regarded as very serious

In 1937 Pund and Greenblatt[17] established granuloma inguinale of the cervix a a distinct clinical entity In this connection Arnell and Potekin[18] 1940 reported an analysis of 38 cases of granuloma inguinale of the cervix which had occurred at Charity Hospital of Louisiana in New Orleans Previously McGee[19]

1934 pointed out that the exuberant granulomatous ulcerations of the cervix, nonmalignant in character might be related to granuloma inguinale Carcinoma of the cervix is easily confused with cervical granuloma inguinale, and in 27 of the 38 cases reported by Arnell and Potekin carcinoma had been diagnosed Vaginal bleeding and pelvic pain were the outstanding symptoms

Extragenital lesions were recognized as early as 1905 by Donovan[4] In fact the case in which he described the ' small forms later called Donovan bodies was an oral lesion This patient and 5 others had been examined with positive results as to finding the small forms' Parounagian and Goodman, 19?2, reported a patient with lesions of granuloma inguinale and syphilis In this instance the granulomatous lesions inguinale involved the upper lip right side of the neck genitals anus and gluteal femoral folds Beeson[1] in 1922 Hunter in 1923 and Hall[?] in 1938 each reported a case with genital lesions and concomitant lip involvement In Hunter s case the pharynx and larynx also were affected Hall noted that depigmentation resulted from the vulva and lip lesions in his case The mouth and face were involved in the patient reported by Sidlik[?], 1927 In Silva s case 1933 the mouth was involved Greenblatt, Torpin and Pund, 1938 estimated the incidence of extragenital cases approximately at 6 per cent Extragenital lesions usually are in association with pudendal lesions All authors agree that there is a similar response to treatment of both types of lesions

Geographic Distribution

The geographical distribution of granuloma inguinale is widespread The earliest cases were reported from India and New Guinea It is endemic in the Solomon Islands New Hebrides Fiji Islands and Northern Australia Case reports from North West and South Africa the Virgin Islands the East and West Indies Southern China Brazil and London England, are indicative of its far flung ramifications That it occurs in tropical sub tropical and temperate latitudes and is a more common affection than is generally supposed, is amply illustrated by case histories from parts of Central North and South America Its endemicity in the United States is emphasized by reported cases from 26 states and the District of Columbia

Incidence

There is a general agreement among those who have studied the disease, that the reported cases by no means represent the true incidence of granuloma inguinale

Race —There is a marked preponderance of the disease among colored patients In an analysis of 150 cases by Fox[14] there were 135 negroes and 15

whites a ratio of 9 to 1 Only 9 8 per cent of 294 cases reported by D Aunoy and von Haam were white Harris , reporting on 195 cases stated the incidence was approximately 4 to 1 It is possible that the respective differences in moral standards and sex hygiene play a significant part

Age —With regard to age the majority of cases range from 0 to 40 years the period of maximum sexual activity The oldest reported case was that of D Aunoy and von Haam a colored woman aged 94 with extensive groin lesions which had been recurrent for 15 years The youngest recorded cases occurred in children aged 6 years and in an infant following circumcision

Sex —It is possible that lesions in the male being more conspicuous and causing greater discomfort as compared with latent deep lesions of the vulva which may remain discreetly hidden for a time influence the males to seek medical aid earlier and with greater frequency At least as judged by the reported cases the males outnumber the females in a varying ratio of 3 to and 2 to 1

Etiology and Pathology

In recent publications there is universal agreement that the demonstration of Donovan bodies either by stained smear or biopsy material from the lesions is the essential finding necessary to establish the diagnosis of granuloma inguinale In the past there has been considerable controversy as to the true etiological agent yet it would seem reasonable to accept as the most probable cause of the disease the one organism Donovan bodies which has been demonstrated with uniformity in the lesions throughout the world

The classification of the Donovan bodies has caused much speculation Three views as to their nature exist (1) that they are a form of Leishmania (2) that they are a species of protozoa but not Leishmania (3) that they are encapsulated bacteria belonging to the capsulated group of bacilli for which the names *Klebsiella granulomatis* or *Microbacterium capsulatum granulomae* have been suggested Cultivation of a capsulated bacillus on Saboaraud s medium has been claimed others have failed to cultivate any organism from the lesions The lesions have been produced in man and in animals by injecting material containing Donovan bodies The capsulated bacillus cultivated from the lesions in man has failed to reproduce the lesion No flagellated forms as in Leishmania have been seen in human or experimental lesions Therapeutic response to fuadin and antimony potassium tartrate favors protozoan grouping The majority of observers favor protozoal rather than bacterial classification and many seem to think it a species or variety of Leishmania

Donovan bodies are ovoid in shape 1 to 3 microns in length and are found in groups clumps or masses both outside and inside the large swollen mononuclear

cells, in leucocytes, fibroblasts and less often in plasma cells These masses or clumped groups are comprised of from 3 to 20 of the organisms They suggest inclusion bodies With Wright's stain they take a pale blue or pinkish stain for the cytoplasm or capsule and a dark blue or deep red stain for the central zone or chromatin They are stained best by Giemsa's stain, the capsule being bright red while the bacterium like central body is dark violet to black The bacillus like structure often appears constricted in the middle and gives the impression of diplococci When they destroy the protoplasm of the phagocytizing cells the cell membrane is ruptured and the bodies are found free in the tissues The organisms are present in greatest numbers deep in the lesions where the disease shows the most advanced pathological changes The Donovan bodies are gram negative

Smears made from the base of biopsy specimens comprise the best material in which to find the organisms A second best but often satisfactory, method is to cleanse the surface of the ulceration thoroughly if bleeding occurs, use gentle pressure until it is controlled then with a knife or curet the surface should be scraped very gently and smears made from the scrapings

The microscopic picture of granuloma inguinale is that of a nonspecific granulomatous reaction with evidence of secondary infection Blood vessel and fibroblastic hyperplasia are indicative of a granuloma, and when infection is present it is an infected granuloma Acanthosis often is of the extremest grade, almost pseudo epitheliomatous at times and bespeaks the long duration of the inflammatory process The fundamental reactive process occurs in the corium in the form of an infiltrate which is composed almost entirely of plasma cells At the same time there is a high grade of capillary hyperplasia associated with the plasma cells A polymorphonuclear infiltrate is only incidental and merely indicates secondary infection There is no tendency toward caseation or the formation of giant cells As the lesions age the cellular elements are absorbed and replaced by fibrous connective tissue This explains the scarred and contracted appearance of the old lesions clinically In preparations stained with Giemsa's stain the intracellular Donovan bodies appear as small clumped central rods which stain from purple to reddish color and are surrounded by a clear zone or capsule outlining the body as an oval shaped structure approximately 3 microns in diameter

Regarding other supposed causes of the disease it was at first thought to be of tuberculous origin At the turn of the century various spirochetes were obtained from the lesions and some observers considered the disease to be due to syphilis Later, cultures were obtained and the organisms were variously termed diplococcoid forms and encapsulated bacilli resembling Friedlander's bacillus mucosus capsulatus However, today despite these controversial claims, the pres

ence of true Donovan bodies are demonstrated with uch regularity in mears and sections that little doubt of the true etiological agent now exists

Symptoms

The clinical appearance of the disease varies greatly in different cases but usually involves in part at least the genitocrural and genitoanal regions The lymphatics are seldom implicated and there is a general absence of constitutional symptoms unless secondary infection or complicating diseases add to the clinical findings Most patients appear with the disease fully developed Chronicity and slowly progressive enlargement of the lesions covering months and even years are striking features of the condition Incipient granuloma inguinale is not troublesome for many individuals and they are prone to absent themselves from medical care for indefinite periods De pite these difficulties an early diagnosis is desirable because the early lesions respond to therapy with greater rapidity than do the advanced lesions

Incipient granuloma inguinale is characterized by small soft bright red, moist finely granular elevations which are not particularly sensitive to manipulation but which bleed easily The bright red velvety surface is especially significant Ulceration commonly is absent at this early stage and there is no evidence of regional lymphatic involvement Occasionally the earliest lesions are small button like papules which may or may not be ulcerated certainly they show little evidence of central healing usually no inflammation and only occasional scar formation at their border These button like lesions may represent initial inoculation sites or a form of propagation in cases of long duration Granuloma inguinale is slow in development but once established it spreads by peripheral extension and autoinoculation with rare signs of healing The outline of the total complex is irregular while that of the individual lesions is uniform and homogeneous

The advanced lesions requiring from months up to 15 years to reach clinical maturity are characterized by indolent superficial serpiginous sclero ing granulomatous ulcerations with raised nodular and irregular borders They are sharply defined against the normal tissue This thickened cicatricial granulomatous mass may completely embed the male genitalia If there is extensive involvement of the penis scrotum or vulva there may be resultant obstruction of the lymph and blood flow which often creates edema and elephantiasis of the affected parts The result of the disea e is more serious for women than men With invasion of the mucosal surface of both the vagina and rectum the lesions become continuous through the thin rectovaginal septum with resultant formation of rectovaginal fistula

Incipient granuloma inguinale of the cervix first appears as soft, red flat granulations They enlarge rapidly developing either a shallow granular ulcer with well defined edges or a hypertrophic granular mass containing multiple small areas of ulceration Eventually the entire cervix may be replaced by a large cauliflower mass of soft friable bleeding tissue These cervical lesions may extend to fill the vaginal vault or may be combined with only a few discrete vaginal lesions or even a single vaginal lesion (Arnell and Potekin) In these cases vaginal bleeding and pelvic pain are the outstanding symptoms

The occurrence of extragenital lesions should be kept in mind They usually appear in association with pudendal lesions and their clinical appearance with regard to onset and development are essentially similar to those involving the genitalia

Diagnosis

The clinical appearance of a chronic persistent granulomatous process involving the groin and genital areas or elsewhere with little or no regional lymph node enlargement is characteristic of the disease The recalcitrant, elevated bright red moist small velvety finely granular lesions which bleed easily and when present the persistent small button like papules are immediately suggestive of the earliest manifestations The demonstration of Donovan bodies in deep tissue scrapings or in biopsy specimens of the affected tissue confirm the diagnosis

Granuloma inguinale is to be differentiated from syphilis chancroid, lymphogranuloma venereum carcinoma of the cervix and chronic streptococcic ulcer One or more of these entities may coexist in the same patient The clinical features of each condition should be kept foremost in mind

Appropriate use of the dark field examination and an intelligent interpretation of approved serological tests for syphilis should be utilized The clinical picture of chancroid is fairly typical and here it is important to rule out a mixed infection with syphilis Stained smears for the Ducrey organisms and the Ito Reenstierna commercial antigen for intradermal testing are to be employed The life long character of a positive Ito Reenstierna test must be kept in mind Lymphogranuloma venereum resembles granuloma inguinale in name only The specific test here is performed intradermally with the Frei antigen The dictum of ' once Frei positive always Frei positive should not be overlooked Histological sections of biopsy material from the lesions will rule out carcinoma However, in this connection the possibility of pseudoepitheliomatous hyperplasia simulating cancer must be emphasized Adequate studies along the above mentioned lines plus proper bacteriological procedures suffice eventually to rule in or out the diagnosis of chronic streptococcic ulcer or other ulcerative lesions

Treatment

The available preparations best used in the treatment of granuloma inguinale are antimony and potassium tartrate intravenously the compound of trivalent antimony and sodium fuadin (stibophen) or anthiomaline intramuscularly and sulfapyridine (M & B 693 2 sulphanilylaminopyridine) orally Locally the treatment may be limited to daily dressings or if deemed advisable surgical excision or irradiation by x ray or radium

The excellent results reported by Farle (1940), when fuadin intravenously and sulfapyridine orally were given simultaneously indicate an almost specific effect of combined action on granuloma inguinale The dosage of sulfapyridine ranged from to 3 grams daily by mouth while that of fuadin ranged from 3 to 5 c c intravenously on approximately alternate days Arthritic pains and other idiosyncrasies to these drugs should be kept in mind

Antimony and potassium tartrate may be administered on alternate days *in doses of 0 03 to 0 12 grams* beginning with *3 c c* and *increasing to 1 c c* of a 1 per cent solution The maximum tolerated dose is most effective in the early phases of the disease and seems to decrease in direct ratio to its duration For the early lesions a 5 per cent sulfathiazole ointment locally and sulfathiazole orally in 0 5 gram doses four times daily frequently exerts a strikingly beneficial effect

All efforts at excision by surgery or destruction by irradiation should completely encompass all cicatrices as well as the granulations and ulcerations since the Donovan bodies are found in the scar tissue and some authorities go so far as to state the disease may recur or propagate from these foci within the cicatrices

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CHAPTER XXX

INFECTIOUS JAUNDICE

By WILBUR A. SAWYER

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Introduction

Synonyms — Epidemic jaundice Weil s disease Spirochaetal jaundice Spirochaetosis icterohaemorrhagica

Definition — An acute infectious disease caused by the spirochete *Leptospira icterohaemorrhagiae* and characterized by fever conjunctival congestion pains in the muscles jaundice hemorrhagic diathesis and albuminuria

History — Although febrile jaundice was observed in epidemics and described by various writers in the Eighteenth and early Nineteenth Centuries it was not generally recognized as a separate entity until 1886 when Weil published his description and discussion of four cases Since then infectious jaundice has been designated commonly as Weil s disease and has been reported from many parts of the world Numerous cases have been found in Europe and during the recent Great War the disease appeared on the Western front in the troops of several nations In Japan the disease long has been recognized and it was there that the causative organism was discovered Recently many cases of a mild form have been investigated intensively in Sumatra

In the United States during the past few years the causative agent has been demonstrated in eight isolated cases, and in Canada one case was reported recently The proven cases however, represent a small part of the jaundice of infectious nature which has been observed Blumer found records of many outbreaks in the United States, the earliest in 1812, and concluded that infectious jaundice had increased considerably in prevalence in recent years He was of the opinion however that the common, non fatal infectious jaundice of the United States is not true Weil s disease and does not have the same exciting organism In a number of instances unsuccessful attempts were made to demonstrate the presence of leptospirae It is, of course, quite possible that the future will show that there are several types of jaundice, which are infectious and due to organisms not yet identified, including some now classed as "catarrhal , but in this chapter we shall use the term "infectious jaundice' as the name of a specific disease caused by the *Leptospira icterohaemorrhagiae*

Etiology

The cause of infectious jaundice was unknown until late in 1914, when Inada and Ido in Japan discovered a spirochete in the liver of a guinea pig inoculated with patient s blood Afterward they found the same organism in the blood and tissues in cases of infectious jaundice and demonstrated that the blood of patients contained a substance destructive to the organism Early in 1915 they announced that Weil s disease was due to this spirochete, which they named *Spirochaeta icterohaemorrhagiae* Later in the same year, in Germany, the organism was discovered independently by Uhlenhuth and Fromme and the transmissibility of the infection to guinea pigs by inoculation of patient s blood was demonstrated also by Huebener and Reiter

Noguchi suggested that this spirochete and others morphologically similar should form a separate genus, named *Leptospira* Accordingly the *Spirochaeta icterohaemorrhagiae* has become the *Leptospira icterohaemorrhagiae* Some European writers still use the name adopted by the early German investigators *Spirochaeta icterogenes*

The discovery of the etiological factor in Weil s disease opened the way for much fruitful study The leptospira of infectious jaundice in Europe was shown by several investigators to be identical with that of the disease in Japan The seven day fever of Japan with resemblances to Weil s disease, was found to be caused by a leptospira differing in its serum reactions from *Leptospira icterohaemorrhagiae* and the newly found organism was classified as a separate species, *Leptospira hebdomadis* A leptospira, isolated from cases diagnosed as yellow fever was regarded by Noguchi as a new species and named *Leptospira icteroides*

The *Leptospira icterohaemorrhagiae* was found to be present in wild rats caught in many parts of the world The organism usually was present in the kidney tissue Such infected rats have been found in various places in Japan Europe the United States and South America in fact almost everywhere that careful and extensive investigations have been made McKinley has recently reported the infection in rats in Manila The percentage of infected rats among those examined in the several countries ranged from 0 to around 40 the higher percentages being found usually where infectious jaundice was common in man In Manila where the disease has not been encountered in man only about one per cent of the rats were infected In connection with their study of Weil s disease in the British army in Flanders, Stokes Ryle and Tytler reported that the spirochete was present in the kidneys of 6 out of 15 rats examined

Leptospirae morphologically indistinguishable from *Leptospira icterohaemorrhagiae* have been found to be widely prevalent in natural waters They are however serologically different from pathogenic leptospirae and have been designated *Spirochaeta pseudoicterogenes* Wolbach and Binger observed a leptospira (*Spirochaeta biflexa*) in water from a pond near Boston in 1914 and in recent years leptospirae have been found in fresh stagnant polluted and even saline waters Hindle demonstrated their presence in London tap-water by mixing a small quantity of human feces with the water incubating at 25° C for 10 to 14 days and examining under the dark field microscope Baermann and Zuelzer added rabbit serum to water specimens in Sumatra to bring about an increase in the lepto pirae present Such cultures could be freed from bacteria by passage through a guinea pig In Nigeria Bauer obtained pure cultures of leptospirae from various water samples by passing them through Berkefeld N filters and then adding guinea pig blood and nutrient agar

It was quite generally considered that the water leptospirae were of species entirely separate from the pathogenic ones until Buchanan in 19 3 produced fatal infection by inoculating two guinea pigs with slime from the roof of a tunnel of a coal mine The animals showed jaundice and hemorrhages and had leptospirae in their organs

The tendency now is to consolidate the known leptospirae into fewer species Sellards and Schüffner and their associates have come to the conclusion that *Leptospira icteroides* is identical with *L icterohaemorrhagiae* Schüffner considers on the other hand that certain pathogenic cultures from Sumatra have only a distant relationship to strains from European Weil s disease A radical position has now been taken by Baermann and Zuelzer who claim that all the known strains of leptospira of the type *L icterohaemorrhagiae* (*Spirochaeta icterogenes*) are identical They have collected cultures of water leptospirae from many parts of the world and have succeeded in making them virulent and in changing their serological characteristics by passing them through animals This ex

perience together with the observation that people frequently are infected by prolonged contact with water, have convinced them that man may become infected with water leptospirae without the intervention of any animal They have found that serological tests are not reliable for subdividing the leptospirae into group as the characteristics are so easily changed by cultural methods and animal passage They have finally reached the conclusion that *Leptospira icterohaemorrhagiae* *L hebdomadis* and the original fresh water *L biflexa* in fact all known pathogenic and water leptospirae of the same type are identical

The *Leptospira icterohaemorrhagiae* is a delicate spiral organism with such fine coils that under the dark field microscope it has a beaded appearance It varies greatly in length but is usually between 6 and 12 μ long and about 0 3 μ thick The ends are tapering and sharp and are hooked to one side or the other When free in a fluid the leptospira is very active It has a rapid rotary motion which gives the slightly bent advancing end a blurred fork like appearance The other end is bent to one side and rotates more slowly The organism can reverse its direction or remain stationary

The *Leptospira icterohaemorrhagiae* can be stained with Giemsa s solution, and in tissues by the Levaditi silver impregnation method It is filtrable through the Berkefeld N candle It grows in media containing blood serum and a little hemoglobin for example the semi solid medium devised by Noguchi It is a strict aerobe, and the growth is heaviest in a hazy plane near the surface of the medium The very first growth may appear however as pale indefinitely bounded globular colonies scattered throughout the medium The optimum temperature for growth is around 27° C The leptospirae are present in the blood stream of patients for the first four to seven days of the illness but are usually too few to be demonstrable by direct dark field observation of the diluted blood If guinea pigs are inoculated with such blood, the leptospirae may become visible in their blood and usually are found easily in the kidneys and liver If a culture of *Leptospira icterohaemorrhagiae* is mixed in equal proportions with the serum of a convalescent from infectious jaundice agglutination will take place and if some of the freshly mixed material is injected into the peritoneal cavity of a guinea pig the Pfeiffer phenomenon may be observed and the animal will be protected from infection

Epidemiology

It is not known definitely how man becomes infected with the leptospira of infectious jaundice Certain facts have emerged however from the growing experience The disease is likely to appear in persons whose occupation involves prolonged exposure to water, as for example soldiers in wet trenches workers

in drainage ditches and coal miners in wet diggings Infection also frequently has followed bathing in streams and long contact with water is regarded by Baermann and Smits in Sumatra as an important factor in infection It is known that the pathogenic organism may persist for some time in water in the presence of bacteria at least 55 days in the experience of Sawyer and Bauer The water leptospirae probably persist indefinitely under similar conditions

The environment of the infected persons often contains numerous rats among which a considerable percentage harbor the *Leptospira icterohaemorrhagiae* in their kidneys and excrete the organisms in their urine Man also excretes the organisms in this way throughout the latter part of the course of the disease and early in convalescence

Leptospirae are found commonly in natural waters or slime In one instance such leptospirae were demonstrated to be pathogenic by direct animal inoculation, and in a considerable number of experiments they have been made pathogenic by passage through animals The organism is able to pass through the intact skin or mucous membranes of guinea pigs and probably of man Ordinary contact infection is rare if it occurs

A lasting immunity usually follows an attack but its duration is not definitely known Baermann and Zuelzer report that the immunity sometimes may be brief

Soon after the discovery of the leptospira in rats it was thought that the organisms entered the human body through food or drink which had been contaminated by rats and that these animals were the natural reservoirs of the disease Later it seemed probable that leptospirae from contaminated water entered through the skin under conditions of prolonged exposure Now it appears more and more probable that the leptospirae living in natural waters are under certain unknown conditions able to enter the human body through the abraded or intact skin or mucous membranes and cause infectious jaundice More evidence will be needed before a decision can be made as to the common method of infection

Pathology

The most characteristic lesions are jaundice hemorrhages and acute inflammation of the kidneys A very complete study of the pathology has been made in Japan by Kaneko and numerous other writers have reported on small groups of cases

Gross Pathology — Intense jaundice is always present in fatal cases Hemorrhages take place through diapedesis in nearly all parts of the body They may be observed as minute hemorrhages in the tissues or as petechiae and ec

chymoses in the skin, mucous membranes and serous membranes The kidneys are severely damaged They are markedly swollen and may show visible hemorrhages The cut surface is bile stained The liver is enlarged in the first and second stages of the disease Later it becomes of about normal size and consistency and takes on a yellowish color The spleen shows little change The lungs may show congestion, and ecchymoses may be seen in the pleurae The stomach and intestines are often the seat of small hemorrhages

Microscopic Pathology — In the kidneys the epithelial cells of the convoluted tubules show cloudy swelling, and some of them may be necrotic Casts are visible in the lumina Fatty degeneration may be present but is not marked Early in the disease the changes in the liver are slight and consist of a little cloudy swelling in the epithelial cells and the necrosis of a few of them Late in the disease the damage to the epithelial cells is more severe There is accumulation of bile pigment in cells near the central vein of the lobule, and some of the cells in this region may become dissociated from each other and necrotic Fatty degeneration is often present but is not extreme It is greatest in the central zone of the lobule Intra alveolar hemorrhages are found in the lung tissue The skeletal muscles especially those of the calf, may show foci of degenerative change and cell infiltration Leptospirae may be seen often in the kidney tissue prepared by the Levaditi method of silver impregnation

Symptoms

The clinical course of infectious jaundice may be divided conveniently into three stages as suggested by Inada the first or febrile stage the second or icteric stage and the third or convalescent stage The first two stages are each about a week in duration and the third may last longer than a week

Incubation — The period of incubation most commonly is from four to seven days, but may be as long as ten

First Stage — The onset is sudden and it is accompanied sometimes by a chill Prominent early symptoms in a typical case are fever (102° to 105° F) severe headache vomiting pain in the muscles with sensitiveness to pressure, pronounced injection of the conjunctiva of the eyeball and prostration On about the fourth day jaundice usually is visible in the conjunctivae but there are some light cases in which jaundice is not noticeable Petechiae are sometimes seen in the skin at this time Nose bleed is not infrequent The tongue has a white or brown coat and red edges On the lips there may be hemorrhagic herpes The liver not infrequently is moderately enlarged but increase in the size of the spleen rarely is observed The urine becomes deeply colored with bile and shows also a small or moderate amount of albumin and some casts Constipation is the rule, but there is sometimes diarrhea After the first day or

two the fever starts to descend in an irregular curve The pulse rate is low in proportion to the temperature in may cases The leucocyte count usually is moderately elevated and there may be a high leucocytosis

The leptospirae circulate in the blood in this stage and are said to be most numerous on the fourth and fifth days They are ordinarily too few however to be seen on direct examination under the dark field microscope but their presence often may be determined by the intraperitoneal inoculation of guinea pigs with the blood The leptospirae disappear from the blood entirely on about the seventh day

Second Stage — In this period the jaundice reaches its climax The headache and muscular pains decrease The hemorrhagic diathesis becomes more prominent and petechiae sometimes are present in the skin The urine contains much bile and a moderate amount of albumin rarely a large quantity There may be marked general weakness Death occurs most often between the eighth and sixteenth day Toward the end of this stage the temperature may reach normal At this time the serum acquires the power to overcome the leptospirae as may be shown by testing it with a culture of *L icterohaemorrhagiae* for the Pfeiffer reaction

Third Stage — In this stage the jaundice lessens and the temperature becomes normal or subnormal In a considerable proportion of cases (28 per cent in Inada s series) an after fever begins a few days after the temperature has reached normal This after fever cannot be regarded as a relapse because there is no return of jaundice congestion of the eyes leptospirae in the blood or of any of the principal characteristic symptoms except fever The temperature remains elevated for three or four days and then slowly falls to normal again Convalescence is slow but there are usually no sequelae

During this stage the leptospirae increase in the urine reaching a maximum between the fifteenth and twenty fourth days and decrease after that until their complete disappearance on about the fortieth day They have been present however as late as the sixty third day In the third stage the only tissues in which the leptospirae may be found are those of the kidneys

Diagnosis

The sudden onset with high fever and prostration the vomiting the intense injection of the conjunctivae of the eyeball and the muscular pain and sensitiveness are early symptoms suggestive of infectious jaundice The appearance in a few days of jaundice of bile and albumin in the urine and perhaps of petechiae in the skin and other hemorrhagic manifestations should make the diagnosis of infectious jaundice seem highly probably To be certain however the infecting organism should be demonstrated by the inoculation of guinea pigs

chymoses in the skin mucous membranes and serous membranes The kidneys are severely damaged They are markedly swollen and may show visible hemorrhages The cut surface is bile stained The liver is enlarged in the first and second stages of the disease Later it becomes of about normal size and consistency and takes on a yellowish color The spleen shows little change The lungs may show congestion and ecchymoses may be seen in the pleurae The stomach and intestines are often the seat of small hemorrhages

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and a culture of *L icterohaemorrhagiae* as already described and the serum may be tested also to find out if it will protect a rhesus monkey against yellow fever virus After death the diagnosis may be established by histological examination The extreme eosinophilic necrosis in the middle zone of the lobules of the liver with breaking up of the columns of epithelial cells as found in yellow fever, is not seen in infectious jaundice Kaneko recently has compared specimens of yellow fever liver from South America with his abundant infectious jaundice specimens He has never found in infectious jaundice the extreme changes which occur in the liver in fatal cases of yellow fever

Prognosis

The mortality varies greatly between different outbreaks In European Weil s disease the mortality has sometimes been as low as 4 or 6 per cent The mortality reported from Japan varied from 30 to 40 per cent Death is rare in the after fever The light cases have a very low mortality

Treatment

For light cases the treatment need only be symptomatic The headache general pains and the constipation will need relief Alkaline waters should be drunk freely For persistent vomiting with danger of acetonuria nutrient enemata containing glucose have been recommended

The more severe cases should be treated with the serum of a horse immunized against many strains of *L icterohaemorrhagiae* Baermann and Zuelzer have found that such a serum gives good results in severe cases when administered early Doses of 50 c c or more should be given as soon as the diagnosis is made and should be repeated as needed at intervals of two or three days

Prevention

As the leptospira is excreted in the urine of patients until about the fortieth day after the onset the urine of infected persons should be disinfected during this period Inada and his associates observing that the disease occurs frequently in certain wet coal mines recommended that the water should be pumped from the places where the men work and that the ground should be disinfected with lime As far as possible conditions should be corrected which would compel the prolonged exposure of laborers in wet clothing to water in drainage ditches sewers and elsewhere Such place also should be cleared of rats as far as possible in order to reduce the contamination of the water and soil with pathogenic leptospirae If these measures fail recourse may be had

with blood taken around the fourth and fifth days or by the dark field microscopic examination of the urinary sediment for leptospirae after the tenth day

Some of the urine and sediment should be injected also into guinea pigs if the inoculation with blood has not been successful Guinea pigs inoculated with material containing considerable numbers of the leptospirae may have fever by the fourth or fifth day after inoculation, and jaundice two or three days later At necropsy they show marked jaundice and conspicuous hemorrhages in the lungs inguinal region and retroperitoneal tissues, and the leptospirae may be demonstrated by dark field examination of scrapings from the liver or kidneys

Beginning with the third stage, the serum may be tested for substances protective against the leptospira In making such a test one cubic centimeter of the patient s serum is mixed with an equal amount of a rich young culture of *Leptospira icterohaemorrhagiae* and one cubic centimeter of the mixture is introduced into the peritoneal cavity of a guinea pig After thirty minutes and again after two hours a drop of the peritoneal fluid is withdrawn and examined under the dark field microscope If abundant active leptospirae are seen at the end of two hours and the guinea pig develops infectious jaundice and dies the test is negative If the leptospirae are absent or motionless and clumped at the end of a half hour and the guinea pig remains well for an observation period for at least two weeks the test is positive Dark field examination of scrapings of the kidneys and liver of the dead guinea pig should reveal leptospirae In making the Pfeiffer test if the fluid obtained by tapping is entirely free from organism there is a possibility that the fluid injected is pocketed and is not being obtained for examination In such cases a test should be made in a duplicate animal and in any event the guinea pig should be kept under observation to see whether it has been protected by the serum

Differential Diagnosis — In *catarrhal jaundice* the onset is not so sudden and severe as in infectious jaundice and the marked injection of the eyes the prostration and the albuminuria are not present *Relapsing fever* is sometimes accompanied by jaundice The type of the fever curve, however is quite different from that of infectious jaundice and the characteristic organism is easily found in the blood

Yellow fever is the disease which is most difficult to differentiate from infectious jaundice and it may be impossible to make the distinction from the symptoms in an individual case The fact that an epidemic of yellow fever is present should not be allowed to decide the diagnosis Ordinarily we do not see the black vomit or the extreme albuminuria of yellow fever in infectious jaundice In some cases the diagnosis will have to be made by blood inoculations of guinea pigs to determine whether the leptospira of infectious jaundice is present or of *Macacus rhesus* monkeys to find out if the blood contains the virus of yellow fever Early in convalescence Pfeiffer tests may be made with the serum

CHAPTER XXX-A

SEVEN-DAY FEVER

By COL. CHARLES F. CRAIG, Medical Corps, U. S. Army
(Retired), D.S.M.

Table of Content

Synonyms.—Nanukayami, Sakusku fever, shueki, autumn fever, harvest fever.

Definition.—An acute infectious febrile disease characterized by a sudden onset, marked prostration, general glandular enlargement and a febrile period lasting about seven days. The disease is caused by a spirochete, *Leptospira hebdomadis*.

History

Seven-day fevers have been described in several countries but it is now well known that different febrile conditions have been included under this term. The name should be restricted to the disease prevalent in certain parts of Japan and Asia to which attention was first called by the Japanese observers Ido, Ito and Wani. In 1917–1918 these observers demonstrated a spirochete in the blood and urine of patients suffering from a fever known as Nanukayami occurring during the autumn in certain parts of Japan, which is now recognized as a distinct disease entity and called seven-day fever. The spirochete was

to the active immunization of persons specially exposed with a vaccine consisting of killed cultures of *L icterohaemorrhagiae*, but the practicability of this method and the degree of the protection obtained has not yet been established adequately by experience

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the field vole *Microtus montebelloi* about 3 per cent of the animals trapped in the endemic regions showing the spirochetes in the urine The endemic regions in Japan correspond to the regions in which this field rodent is found and man contracts his infection either through the bite of the voles or through contamination of food or drink with the urine of these animals Hence it follows that the disease is almost entirely confined to laborers in the fields and forests of the endemic regions The field vole often improperly called the field mouse, which transmits this disease burrows in the ground and lives upon grain nuts and roots While the field vole is the reservoir of infection for man it should be remembered that *Leptospira hebdomadis* occurs in the urine of convalescents from seven-day fever for several weeks and that such urine is infective The practice of using urine for fertilizing purposes, which is common in the endemic regions in Japan, undoubtedly assists in transmitting the infection

Pathology

Nothing is known of the lesions which may be produced by this disease as it is never fatal and there are no autopsy records available The fact that the spirochetes are excreted in the urine for several weeks after the fever has disappeared and that during the febrile period albumin often occurs in the urine would indicate that the kidneys bear the brunt of the infection

Symptomatology

The period of incubation is uncertain but short and the symptomatology is much like that of dengue fever The onset is sudden with a slight chill or chilly sensations marked aching of the muscles especially those of the legs and back headache supra-orbital in location anorexia nausea marked prostration and general enlargement of the lymphatic glands The conjunctivæ are injected and in rare cases slight jaundice may develop The muscles especially those of the calves are tender upon pressure and there may be hyperæsthesia of the skin in limited regions The face appears flushed the eyes brilliant and there is marked mental depression In some cases a measles like eruption has been noted upon the fore arms but this is in no wise characteristic of the disease and may have been confused with the eruption of dengue The spleen and liver are not enlarged During the first three days of the disease there is a marked leucocytosis which is succeeded by a moderate decrease in the number of leucocytes Albuminuria is common during the fever

The temperature curve usually shows an abrupt rise to 103 F (39 4 C) or 104 F (40 C) after which it remains remittent until the seventh day when it subsides by crisis and the attack is over In mild cases there may be fever

named *Leptospira hebdomadis* by Ido, Ito and Wani and is now generally accepted as the cause of the disease

Geographical Distribution

It is more than probable that the geographical distribution of seven-day fever is much more extensive than is generally supposed To date it has been found in certain localities in Japan China, India, Arabia and the Netherland Indies and somewhat similar fevers, caused by similar spirochetes, have been described as occurring in the Federated Malay States by Fletcher (1928) and in Sumatra by Vervoort (1923) The disease has been known in Japan for many years and it is in this country that most has been accomplished in the study of its clinical nature and etiology

Etiology and Epidemiology

Ido Ito and Wani (1917–1918) found a spirochete in the blood and urine of patients suffering from this disease (known in Japan as Nanukayami) which they named *Leptospira hebdomadis* This leptospira when inoculated into young guinea pigs produced an infection characterized by glandular enlargement and slight jaundice in about 17 per cent of the cases with a mortality in the guinea pigs of about 60 per cent In this respect the infection in the guinea pigs somewhat resembles Weil s disease but guinea pigs inoculated with *Leptospira icterohemorrhagiæ* the cause of Weil s disease develop jaundice in 99 per cent of the infections and the mortality is 100 per cent The leptospira is present in the blood of man during the period between the second and seventh day of the disease and can be demonstrated by the dark field or by blood smears stained with the Wright or Giemsa stain but in very small numbers In infected guinea pigs the leptospira occurs in the blood and viscera After the seventh day of the fever and for four to five weeks after the crisis the leptospira may be found in the urine of patients *Leptospira hebdomadis* may be cultivated upon suitable media and is said by Zuelzer and Oba (1923) and Noguchi (1925) to be morphologically distinguishable from *L icterohemorrhagiæ*, being longer thicker and more refractile Serologically it can be distinguished from other spirochetes and if the blood of convalescents from the fever be injected with a culture of the leptospira into the peritoneal cavity of guinea pigs a positive Pfeiffer reaction occurs Immunity follows an attack of the disease in most individuals

Seven day fever occurs in Japan during the months of September and October the harvest months hence the fever is sometimes called 'autumnal fever or harvest fever The natural reservoir of the infection in Japan is

Prognosis

The prognosis is excellent There is no record of death following an attack of seven-day fever nor do complications or sequela of consequence occur

Prophylaxis

Prophylaxis consists in the proper protection of food and drink from contamination by the urine of patients or the field voles, which serve as reservoirs of the virus and avoidance of the endemic areas of the disease If one should be bitten by a field vole, the prompt and vigorous application of tincture of iodine to the wound might prevent infection, or cauterization with carbolic acid

Treatment

The treatment of seven-day fever is purely symptomatic The infection i self limited and of no danger to life so that other treatment is not indicated It is probable that injection of the ar pheramines would prove curative but, owing to the benign nature of the disease such treatment would not be justifiable

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for a day or two only, and in some patients there is apparently a saddle back type of temperature curve Here, again, dengue may have been confused with seven day fever In the vast majority of cases the fever lasts for approximately seven days and does not recur Convalescence is rapid, but there may be considerable prostration for a week after the crisis of the fever

Complication and Sequelæ

The disease being of mild character with no mortality and of short duration is not characterized by any complications or sequelæ of importance Slight bronchitis has been noted in some cases, and secondary anemia is described as occurring not infrequently

Diagnosis

Seven-day fever has been confused most often with dengue, Weil's disease relapsing fever and a disease known in Japan as Akayami, or harvest sickness.

It would probably be impossible to differentiate this fever from mild dengue infections but in the typical case of dengue the greater muscular pain, the saddle back temperature and the characteristic eruption should serve to distinguish it from seven-day fever Relapsing fever should be easily distinguished by the occurrence of the relapses while Weil's disease may be differentiated by the common occurrence of jaundice a symptom almost always absent in seven day fever by the longer continuance of the fever and by the results of guinea pig inoculation with the blood already mentioned The differentiation from Akayami is exceedingly difficult as the symptomatology of the two conditions are practically the same In fact the two infections appear to occur in the same localities at the same time and the distinction must be made upon the characteristics of the spirochetes associated with them In Akayami a spirochete has been demonstrated by Kitamura and Hara (1918) as the cause of the disease and called *Leptospira autumnalis* In guinea pigs this spirochete produces jaundice and hemorrhages in the nasal genital and anal regions and death occurs in from four to five days after inoculation of blood or cultures, while guinea pigs inoculated with *L hebdomadis* do not show marked jaundice or hemorrhages and recovery occurs in about forty per cent of the infected pigs

As the spirochetes occur in the blood in very small numbers a diagnosis is sometimes impossible from a microscopic or dark field examination of the blood alone and cultures should be made of the blood upon Noguchi's medium or guinea pigs inoculated either intraperitoneally or subcutaneously with the blood of the patient The organisms may be found in the blood urine and viscera of the infected guinea pigs

Prognosis

The prognosis is excellent There is no record of death following an attack of seven-day fever nor do complications or sequela of consequence occur

Prophylaxis

Prophylaxis consists in the proper protection of food and drink from contamination by the urine of patients or the field voles which serve as reservoirs of the virus and avoidance of the endemic areas of the disease If one should be bitten by a field vole the prompt and vigorous application of tincture of iodine to the wound might prevent infection, or cauterization with carbolic acid

Treatment

The treatment of seven-day fever is purely symptomatic The infection is self limited and of no danger to life so that other treatment is not indicated It is probable that injection of the arsphenamines would prove curative but owing to the benign nature of the disease such treatment would not be justifiable

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CHAPTER XXX-B

RAT BITE FEVER

By COL CHARLES F CRAIG MEDICAL CORPS
U S ARMY (RETIRED) D S M

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Synonyms —Sodoku (Japanese) Rattenbisskrankheit (German)

Definition —An acute infectious disease characterized by a sudden onset, a characteristic exanthem a relapsing fever lymphangitis and local enlargement of the lymphatic glands It is transmitted by the bite of infected rats and certain other animals and is caused by a spirillum called *Spirillum minus*

HISTORY

According to Robertson (1931) rat bite fever was first described by Wilcox and by Watson in America but they did not investigate the etiology of the disease In 1912 Hata demonstrated that salvarsan was a specific and in 1915 Futaki Takaki Taniguchi and Osumi discovered a spiral organism in animals and patients suffering from the infection which they called *Spirochaeta morsus muris* and which they demonstrated as the cause of the infection The same parasite had been described by Carter in 1887 who found it in rats in India and called it *Spirillum minor* a name afterwards corrected to *Spirillum minus* As the subsequent studies of Zuelzer (1921) Robertson (19 4) and

others have shown that this organism is not a spirochete but a spirillum, and that it is identical with the spirillum described by Carter, the specific name should be *Spirillum minus* Carter, 1887, instead of the name given it by Futaki and his colleagues

Geographical Distribution

Rat bite fever is much more common in Japan than in other countries owing to the greater amount of infection among the rats and the closer association of man and these rodents owing to the peculiar construction of human habitations The disease has a world wide distribution, however, and cases have been observed in England Spain France, Germany, Italy, India, Turkey, Siam, Syria Netherlands Indies China, North and East Africa, Australia the West Indies Brazil, Mexico and the United States

Etiology

Futaki (1915) and his co-workers found *Spirillum minus* in the tissues in the vicinity of the bite of infected rats and in the neighboring lymph glands and produced the disease experimentally in white rats guinea pigs and monkeys In patients the spirillum is found in the exudate from the initial bite in the juice from the adjacent lymphatic glands and in the serum obtained by scarifying the eruption During the fever the spirilla may be found in the peripheral blood but in very small numbers In experimentally infected guinea pigs mice and rats the spirilla may be found in the blood during the first two weeks of the infection and afterwards in the connective tissue, especially in that of the lips and tongue It is rarely found in the urine

The morphology varies greatly short forms containing only two spirals and long forms containing as many as eight or ten are observed in the same specimens Flagella are present at one or both ends The organisms stain with the Wright or Giemsa stain but better results are obtained with the Fontana or silver impregnation methods of staining It can be cultivated according to Futaki upon special media but others have failed to confirm his results in this respect although numerous observers have confirmed the results of the Japanese investigators regarding the causative relation of *Spirillum minus* to rat bite fever Successful cultures have been obtained upon the Noguchi medium

An infection caused by a streptothrix sometimes follows the bite of rats or other rodents which should not be confused with rat bite fever In 1914, Schottmuller isolated two species of Streptothrix *S muris ratti* and *S taraxeri cepapi* in two cases of fever following the bite of a rat and a squirrel respec

tively, and a similar streptothrix was cultivated by Blake in 1916 from the vegetations of an ulcerative endocarditis following a rat bite Tunnicliff in 1916 described a somewhat similar infection in man following a rat bite and others have confirmed these observations It is evident that this infection may be confused with true rat bite fever and it should be borne in mind in the diagnosis of fevers following the bite of rats or other rodents

EPIDEMIOLOGY

Rat bite fever usually is transmitted to man by the bite of infected rats but the bites of infected mice cats dogs squirrels ferrets and weasels have caused the disease in man and the scratches of these animals may also convey the infection In Japan about three per cent of house rats have been found infected and in that country the field vole *Microtus montebelloi* is a common vector of the disease

While rats transmit the infection by biting the spirilla cannot be found in their saliva and it is believed that infection occurs through rupture of the tissue of the rat s lips and mouth in biting as the spirilla occur in the tissues The observations of Mooser (1924) and of McDermott (19 8) have demonstrated that in infected rats the eyes are markedly affected and that the lachrymal secretion is increased greatly in amount and contains the spirillum In addition the sputum of rats having lesions in the mediastinal lymph glands lungs and bronchi is infective although it may be difficult or impossible to demonstrate the spirillum in the secretions Theiler (1926) and Schockaert (1928) have produced the disease in man by inoculation of *S minus* obtained from infected man and Schockaert has also produced the disease in man with *S minus* obtained from a naturally infected rat One attack of the disease apparently confers immunity and substances lytic to *S minus* may be demonstrated in the blood of those who have recovered from the infection

PATHOLOGY

Post mortem examinations of individuals dying of rat bite fever have shown degenerative changes in the spleen kidneys and liver an increased amount of cerebro spinal fluid and marked hyperemia of the cortex of the brain

SYMPTOMATOLOGY

The incubation period varies from five to forty days the average being from ten to twenty seven days after receiving the bite

The onset is sudden with a chill or chilly sensations severe headache nausea

marked prostration, rapid pulse and a sudden and marked rise in temperature At the same time the scar of the healed bite becomes swollen, red, edematous and tender the lymphatics leading from it inflamed, and the adjacent lymphatic glands become enlarged The muscles in the vicinity of the bite may be indurated and edema may develop in the hands, arms or legs Vesicles may form over the healed bite or necrosis of the scar tissue may occur As the disease progresses symptoms connected with the nervous system become prominent, consisting of severe headache photophobia, tinnitus, dizziness and localized areas of hyperasthesia or anasthesia but such symptoms may be almost entirely absent in the mild cases of the disease Constipation or diarrhœa may be present, and there is usually much muscular pain, especially in the arms, legs and back Albumin and casts sometimes appear in the urine

The fever rises rapidly to 103° F (39 4° C) or 104° F (40° C) reaching its fastigium within twenty four hours and remains at approximately this level for from two to three days, when it falls by crisis reaching normal or below in a few hours accompanied by profuse perspiration In mild cases the fever may not be noticeable or may not exceed 101° F (38 7° C) During the first febrile period, but sometimes not until a succeeding one the characteristic eruption appears, maculo papular in type, dusky red or purplish in color, and occurring in irregular areas varying in size upon the trunk or extremities A hot bath may bring out the eruption during the febrile period or even during the afebrile intervals This exanthem is very characteristic and, together with the relapsing fever and changes at the site of the bite practically diagnostic of rat bite fever A secondary anemia of mild degree is present in most cases

After a fever free interval varying from three to seven days, usually six to eight days, during which there have been no symptoms of the infection, there is an acute exacerbation of all of the symptoms mentioned and this sequence of events continues until the patient has had from six to twelve paroxysms, the disease sometimes lasting for several months The symptoms of each paroxysm are usually less severe than those of the preceding one the febrile periods are shorter the afebrile periods longer, and eventually the paroxysms cease or death occurs

During the febrile periods there is a leucocytosis the white cells numbering from 10 000 to 20 000 per cu mm while during the afebrile periods there is a relative increase in the mononuclear leucocytes Eosinophilia is present during the afebrile periods and persists for some time after the final disappearance of the paroxysms The Wassermann reaction is said to be positive in about 50 per cent of the cases

The local symptoms in the region of the bite recur with each access of fever but decrease in severity as the disease progresses until they entirely disappear, and the site of the bite is marked by a bluish red or purplish scar

Complications and Sequelæ

Complications and sequelæ are very rare. Secondary infection of the rat bite is sometimes noted followed by septicemia or pyemia but this is not of frequent occurrence. Bronchitis, broncho-pneumonia and enteritis have been reported as complications. No sequelæ of importance has been recorded.

Diagnosis

The occurrence of a relapsing type of fever following the bite of a rat or other rodent known to transmit the disease after a period of one to six weeks would suggest the diagnosis of rat bite fever and if this fever were accompanied by the local symptoms noted as occurring at the site of the bite and by the characteristic exanthem, a diagnosis can be made from the history and clinical picture alone. Mild cases do occur in which the exanthem is absent and there may be but one or two paroxysms of fever and it is in such cases that the greatest difficulty in diagnosis occurs.

The spirilla are present in very small numbers in the blood during the febrile period and are best demonstrated by the dark field although they may be found in blood smears stained by the Wright, Giemsa, Fontana or silver impregnation methods. The examination of gland juice obtained by gland puncture may result in the demonstration of the organism. If the spirilla cannot be found, a mouse should be inoculated subcutaneously or intraperitoneally with blood obtained from the patient at the time of the febrile period. In from three to fifteen days, usually in eight or ten days, the spirilla may be found in the peripheral blood of the inoculated animal.

Prognosis

In Japan the mortality of rat bite fever is about 10 per cent, but in other countries it has been much less. In the United States and Europe the mortality has been but a small fraction of one per cent.

Prophylaxis

The prophylaxis consists in the destruction of rats and their breeding places, protection from their bites and the prompt cauterization of the bite with carbolic acid.

Treatment

As shown by Hata in 1912, the arsphenamines act as specifics in rat bite fever, and the disease is easily cured with from two to three injections of arsphenamine or neo arsphenamine, the dose varying from 0 3 gm to 0 45 gm During convalescence strychnine iron and arsenic are useful as tonics Until the disease is controlled by the arsphenamines treatment should be purely symptomatic

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CHAPTER XXXI

YELLOW FEVER

By WILBUR A SAWYER

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DEFINITION

Synonyms —Typhus icteroides yellow jack black vomit typhus amaril vomito negro vomito prieto

Definition —Yellow fever is an acute febrile infectious disease characterized in typical cases by sudden onset prostration a pulse rate slow in relation to temperature vomiting of altered blood albuminuria and jaundice It is transmitted from man to man by the mosquito *Aedes (Stegomyia) aegypti* and occurs chiefly in tropical and subtropical countries in localities where this mosquito abounds Many cases of yellow fever including numerous mild ones are without most of the symptoms mentioned and can be diagnosed only by laboratory tests More over the endemic and epidemic disease has been found to occur in certain regions with forest environment in the complete absence of aegypti mosquitoes and the evidence is accumulating that other mosquitoes transmit the disease under such conditions and that other animals than man especially monkeys may become infected may multiply the virus and may infect bloodsucking insects

History

Origin —Little is known of yellow fever before the discovery of America by Columbus. Some hold that America was the original home of the disease and support their claims by references to Maya records of ancient pestilences of black vomit. Others have concluded that the disease is of West African origin and was imported into America in the early slave trade. The African origin seems more probable. It is certain, however, that yellow fever was prevalent in the West Indies early in the seventeenth century and was distributed from there by sailing vessels to many ports of America and Europe.

Distribution —Yellow fever appeared at times in France and England but as a rule only among persons associated with the ships which brought the infection. Probably it was introduced also into Italy and several other countries of Southern Europe, but the principal epidemics of recognized yellow fever in Europe occurred in cities of Spain. In Barcelona some 20 000 persons were said to have died in the yellow fever epidemic of 1821.

North America has suffered repeatedly from yellow fever introduced from the West Indies by ships. The larger ports on the Gulf of Mexico and along the Atlantic seaboard were invaded often and the disease extended up the Mississippi valley as far as southern Illinois. Some of the largest epidemics were those in New Orleans in 1878 (4 046 deaths) and in Philadelphia in 1793 and 1803 (4 044 and 3 900 deaths respectively). In 1803 there was an epidemic in New York with 606 deaths. In South America the disease has been serious in ports on the Atlantic, Caribbean and Pacific coasts. In Rio de Janeiro about 60 000 persons died from yellow fever between 1850 and 1905. In Guayaquil there were over 20 000 cases in the 8¼ years preceding 1904. In Central America and the West Indies outbreaks in former times were frequent and severe. Havana was one of the important seed beds from which the infection was distributed. As far as is known, the Orient always has been free from yellow fever, although the mosquito capable of conveying the disease is distributed widely there in the warmer countries.

In recent years yellow fever apparently has existed only in Africa, South America and Panama east of the Canal Zone. Few of the present generation can appreciate the relief which has come to many communities of the southern United States through freedom from the terror of threatened epidemics, from shot gun quarantines and from serious restrictions on commerce. The factors chiefly responsible for the great reduction in the threatened areas are two: the effective control measures which followed the discovery at the beginning of the century that the mosquito *Aedes aegypti* was solely responsible for the spread of yellow fever in the then known endemic and epidemic regions and the

replacement of wooden sailing vessels with their larva infested casks and tanks by iron steamships with closed water containers

In West Africa the disease has long been present and the amount of epidemic yellow fever fluctuates considerably from year to year Since the latter half of the eighteenth century yellow fever has been recognized in this region and has struck down European sailors traders and officials and Syrian traders but for many years it was seldom reported in the natives Recent investigations have brought to light epidemics of considerable size in native negro communities but with a decidedly lower mortality than occurs among white persons In 1927 there was much yellow fever in many countries from Senegal to the Belgian Congo Since then scattered outbreaks have been recognized in West Africa In Central and East Africa the presence of yellow fever was not definitely established until yellow fever immunity was discovered in wide areas through the examination of human blood specimens by mouse protection test in the extensive surveys of 1933 to 1935 All doubts of the significance of the findings were dispelled in 1940 when the largest yellow fever epidemic ever recorded for Africa occurred in the Nuba Mountains Anglo Egyptian Sudan with 15 000 cases Africa seems to be free of yellow fever north of the Sahara in the far south and in the eastern coastal region

In the Western Hemisphere for many years prior to 1900 the disease was present almost constantly in several large and important cities from Vera Cruz and Havana in the north to Rio de Janeiro in the south and was intermittently epidemic in a larger area The most important epidemic of recent years occurred in Rio de Janeiro in 1928 and 1929 and comprised 738 cases with 435 deaths That city had been practically without cases of local origin since it was freed by control measures under Oswaldo Cruz twenty years earlier Other recent outbreaks occurred in 1929 in Socorro Colombia and in 1932 in Santa Cruz de la Sierra Bolivia and were of special interest as the origin of the infections was a mystery at the time More recently outbreaks of jungle yellow fever have been observed in several countries of South America particularly Brazil and Colombia The last recognized epidemics in Central and North America occurred in 1924 in Salvador and in 1922 in Mexico

Recognized epidemics and typical severe cases gave a very incomplete picture of the distribution of yellow fever infection as was shown from 1931 to 1937 by the world wide survey of acquired immunity Many thousands of human blood specimens were collected and tested by the intraperitoneal protection test technique for their power to protect highly susceptible strains of white mice against yellow fever virus

The results have been summed up in publications by Sawyer and Whitman Sawyer Bauer and Whitman Soper and others It was found that the Orient

Europe, North East coast and South Africa, Australia and Canada were essentially devoid of yellow fever immunity in man. In the United States it was necessary to search out aged persons with a history of having had yellow fever many years before in order to find immunes. In Mexico, Central America west of the Canal Zone, the West Indies, South America west of the Andes and the northern littoral of South America immunity was limited to persons old enough to have acquired yellow fever during former known epidemics or soon afterward. The highly significant result of the world survey was the discovery of two great endemic areas in Africa and South America, previously unsuspected in most of their extent. The African area of yellow fever immunity in man, as determined by blood tests in mice, is widely but irregularly distributed from the coast of Senegal eastward for about 3,300 miles to the upper reaches of the Nile in the Anglo-Egyptian Sudan and probably somewhat farther. On the north the region is limited by the Sahara Desert and on the south the boundary, though not so clear cut, lies at about 6 degrees south latitude. The western part of the area, up to the eastern boundary of Nigeria, had been recognized previously as infected, but the eastern part, except to the south on the Atlantic coast, had never been suspected of harboring the virus of yellow fever.

In the Western Hemisphere, where yellow fever was widespread within the lifetimes of the older members of the present generation, the approximate area of endemicity was ascertained by finding out where young people were immune by intensive field investigation and by the examination of liver specimens obtained by means of the viscerotome from persons dying after an illness of not over ten days. A vast previously unsuspected reservoir of infection thus was discovered. In general it includes the Amazon basin, part of the interior of Colombia, the southeastern part of Venezuela and other regions adjoining the Amazon basin on the north and the south. At present the principal seaports and riverports of the world are free from yellow fever, but there is considerable apprehension that the infection may spread from the endemic areas to centers of travel and be transported by airplanes to distant infectible cities, unless adequate control measures are maintained. Since 1938 there have been no important outbreaks of aegypti transmitted yellow fever in the Western Hemisphere.

Investigation and Control. — The theory of Dr. Carlos Finlay of Havana that yellow fever is propagated by the mosquito was announced in 1881 but received little attention at that time. In 1898 Dr. H. R. Carter of the United States Marine Hospital Service observed at Orwood and Taylor, Mississippi, that a considerable interval elapsed after the development of a first case of yellow fever in a house before the environment became infective, and he called this unexplained interval of ten to seventeen days the extrinsic incubation period. In 1900 the Yellow Fever Commission of the United States Army, composed of Dr.

Walter Reed president, and Doctors Carroll Agramonte and Lazear performed experiments in Cuba which proved conclusively that the mosquito *Aedes aegypti* formerly known as *Stegomyia fasciata* or *calopus* is capable of transferring the causative agent of yellow fever and that an interval of about twelve days must elapse after the mosquito receives infective blood before it can transmit the infection They demonstrated also that the disease could not be transmitted by fomites They proved that the *Bacillus icteroides* of Sanarelli was not the cause of yellow fever and announced that the specific cause remained to be discovered Certain properties of the unseen agent were determined however it was in the circulating blood of patients during the first three days of the disease in diluted blood serum it could be filtered through a Berkefeld cylinder capable of holding back *Staphylococcus aureus* it was destroyed or markedly attenuated by heating at 55° C for ten minutes These findings were made under difficulties for no susceptible animal was known at that time and the only available subjects were human volunteers In spite of this serious limitation to the number of observations the experiments were so well planned and controlled that the essential findings still hold good Of the members of the Commission Lazear lost his life from yellow fever and Carroll had a severe attack of the disease The French Commission (Marchoux Salimbeni Simond) which went to Rio de Janeiro in 1901 confirmed the findings of the Reed Commission and made many additional observations with regard to yellow fever and its vector

No time was lost in applying the new knowledge to the control of yellow fever At the beginning of 1901 Havana was thoroughly infected and contained many non immunes Nevertheless through measures aimed at the mosquito Major Gorgas was able to rid the city of yellow fever by September of that year and for the first time in 150 years there were no cases Under Gorgas the Panama Canal Zone and neighboring cities were freed of the disease by 1905 In Rio de Janeiro Oswaldo Cruz undertook in 1903 to clear the city and completed the task in 1908 The disease was eradicated from Guayaquil in 1918 and 1919 by M F Connor and control work in Peru was completed by Henry Hanson in 1921 Other areas were freed and as the disease was suppressed in the principal disseminating ports it cleared up in many other places spontaneously or with moderate efforts at control

An animal susceptible to yellow fever and suitable for laboratory studies was finally found and experimentation thereafter could be carried on without the use of human subjects In 1927 in West Africa Drs Stokes Bauer and Hudson of the West African Yellow Fever Commission of the Rockefeller Foundation succeeded in transmitting yellow fever by injecting blood from native patients into Asiatic monkeys of the species *Macacus sinicus* and *Macacus rhesus* They transmitted the infection from monkey to monkey by means of blood injec

tions or by bites of mosquitoes of the species *Aedes aegypti* and they demonstrated that the yellow fever virus obtained in Africa is filtrable The chimpanzee and several local African monkeys were found to be resistant to yellow fever Serum from Africans convalescent from yellow fever had a high protective power against the experimental infections The clinical course of the disease in monkeys and the lesions produced were similar to those of yellow fever in man

Working with the experimental disease in monkeys, Bauer and Hudson showed that the virus in the mosquito is transmissible through inoculation during the period of incubation in the insect, when infection cannot occur through biting In one instance yellow fever was transmitted by the bite of the mosquito after only nine days incubation in the insect, but in two other experiments the minimum period was around twelve days Yellow fever was produced in some instances by placing infectious monkey blood on the intact skin of monkeys, and this may help explain the deaths of laboratory investigators

After the discovery of the susceptibility of *Macacus rhesus* yellow fever was transmitted from man to monkey in Senegal by Mathis, Sellards and Laigret, and Sellards transported the virus in frozen liver to England and later to America In the 1928 epidemic in Rio de Janeiro Dr Aragao of the Oswaldo Cruz Institute succeeded in transmitting yellow fever from man to monkey by injection of blood and by the bites of mosquitoes

On account of the impracticability of maintaining strains of yellow fever virus in monkeys and mosquitoes and the difficulty of transporting and storing the virus experiments in virus preservation were undertaken by Sawyer, Lloyd and Kitchen They found that yellow fever virus if thoroughly dried under vacuum in the frozen state and sealed in glass tubes could be preserved almost indefinitely One of their earliest dried specimens sealed in glass in the presence of calcium chloride was tested in a monkey after 10 years of storage at temperatures a few degrees above 0° C and was found to be fully virulent

By means of cross immunity tests in monkeys Sawyer Kitchen, Frobisher and Lloyd showed that the yellow fever now in South America, the present yellow fever of Africa and the historic yellow fever of Panama and other American countries are all one disease One of the soldier volunteers who contracted yellow fever in Walter Reed's experiments in Cuba, contributed a blood specimen 30 years later which protected susceptible mice against an African strain of yellow fever virus

The important discoveries were made by Theiler in 1930 that mice are susceptible to yellow fever virus if inoculated intracerebrally and that immune serum would prevent the infection if injected with the virus The perfection of the intraperitoneal protection test in mice by Sawyer and Lloyd made possible

the world wide yellow fever immunity survey described above, and also facilitated research in immunization by making it practicable to test quantitatively the serum of vaccinated monkeys and persons for the protective antibodies produced

The danger of working in the laboratory with yellow fever virus proved to be great Hideyo Noguchi William Alexander Young Adrian Stokes Paul A Lewis and Theodore B Hayne succumbed to laboratory infections Including these five fatal cases Berry and Kitchen collected records of 32 cases of yellow fever contracted in laboratories after animals became available for use in yellow fever experimentation The situation became so serious that the devising of an effective preventive vaccine became a matter of first importance The steps through which this was accomplished will be given in the section on Prevention The need for vaccination was increased by the discovery that infection with yellow fever occurs in forest areas in the absence of *Aedes aegypti* and under conditions that make vaccination of exposed humans the only practicable control measure at the present state of our knowledge The discovery and study of this "jungle yellow fever" will be discussed in the section on Epidemiology

Epidemiology

Aegypti transmitted Yellow Fever — In all infected cities and in some rural areas yellow fever is transmitted from man to man by the mosquito *Aedes aegypti* and no other vector or animal host has been incriminated in these places Under these circumstances the epidemiology is much as formulated by Carter and Gorgas and aegypti-control is rapidly effective in suppressing the disease In cities in which yellow fever formerly was long present there were many immune persons and the disease tended to burn itself out and disappear because of the scarcity of susceptible persons and the lack of persons in the brief infective stage of the disease to supply virus to the mosquitoes In cities which were constantly or frequently infected the disease could not appear as spectacular epidemics and was observed chiefly in non immune travelers and in scattered children and adults of the locality who had not been immunized previously through infection Most of the infections in yellow fever outbreaks are mild and not clinically recognized though their occurrence can be detected by tests for the subsequent appearance of protective antibodies in the blood In African negroes the case mortality usually is lower than in Europeans or Asiatics

The old time urban yellow fever epidemics were intimately related to shipping The infection frequently was introduced by ships on which it had been maintained by mosquitoes bred on board Often the recognized cases in an outbreak in a partially immune community were grouped mostly about the water

front or were related to the minor shipping In cities of non immunes the introduction of yellow fever in the presence of abundant *Aedes aegypti* resulted in the devastating epidemics of history In the temperate zone such outbreaks often were seasonal and were not terminated until cold weather limited the activity of the mosquito delayed its becoming infective and finally caused it to disappear The domestic habits of the aegypti mosquito rendered it particularly well fitted for transmitting yellow fever, as the larval stages were passed chiefly in artificial containers in or near human habitations This mosquito bites in the daytime and is most aggressive in the early morning

In certain rural areas, for example in northeastern Brazil, *Aëdes aegypti* was sufficiently prevalent to permit the persistence of yellow fever without reinfection from large towns or cities This was evidenced by the failure of the disease to disappear spontaneously when it had been completely eradicated from the large communities It vanished however, when the mosquito control was extended to the rural settlements

Persons with yellow fever transmitted by aegypti have a characteristic age and sex distribution suggestive of the acquisition of the infection in the home or other gathering place As shown by blood tests for protective antibodies males and females are infected almost equally, many infections occur in childhood, and the percentage of immunes usually rises steadily up to a high level, sometimes 70 to 80 per cent, in the age period 20 to 29 years and then remains at about this level as Soper has shown in Brazil

Jungle Yellow Fever — Under certain environmental conditions found in and near tropical forest yellow fever occurs in the complete absence of *Aedes aegypt* and then it is called jungle yellow fever This is the same disease as the yellow fever transmitted by aegypti in urban or rural areas, when classified by clinical or serological characteristics, but its epidemiology is essentially different from this form of yellow fever

That such an epidemiological type of yellow fever exists was not suspected until 1932, when the investigation of an outbreak of yellow fever in the Valle do Chanaan in the State of Espirito Santo Brazil showed that aegypti mosquitoes were not present although mosquitoes, previously shown in laboratory experiments to be capable of transmitting the disease, were found in the locality Later yellow fever immunity, yellow fever diagnosed post mortem by liver examination and frank outbreaks of yellow fever were found in many places in South America in the absence of aegypti mosquitoes

It has been found out by laboratory workers that a number of mosquitoes other than *Aedes aegypti* are capable of transmitting yellow fever by bite Such species are in Africa, *Aedes luteocephalus Aedes stokesi Eretmopodites chrysogaster Aëdes vittatus Aedes africanus Aedes simpsoni Aedes taylori, Aedes*

metallicus Mansonia africana and *Culex thalassius* in South America *Aedes scapularis Aedes fluviatilis Hæmagogus capricornii* and *Aedes leucocelænus*, in the East Indies *Aedes albopictus* in Europe *Aedes geniculatus* In North America yellow fever has been transmitted to monkeys also by *Aëdes triseriatus* in the laboratory under rather abnormal conditions At first it was doubted that these observations had any epidemiological significance It is known, however, that two species of wild caught jungle mo quitoes (*Aedes leucocelænus* and *Hæmagogus capricornii*) from an epidemic area in the State of Rio de Janeiro harbored yellow fever virus in their bodies when captured and transmitted the infection to monkeys *in the laboratory by bite (Shannon Whitman and Franca)* Likewise wild-caught pecimens of *Hæmagogus capricornii* in Colombia, South America and of *Aedes simpsoni* in Africa were found to contain yellow fever virus and *Hæmagogus capricornii* found infected in nature gave yellow fever to monkeys by biting

The evidence is increasing that at least in certain regions wild monkeys play the dominant role as vertebrate host in jungle yellow fever Evidence that various species of monkeys acquire immunity in nature as shown by the presence of protective antibodies in their blood is abundant in areas of South America and Africa in which jungle yellow fever occurs More conclusive evidence was obtained in 1944 in Brazil when yellow fever virus was isolated for the first time from the blood of wild vertebrates caught out in the jungle these were four sick monkeys of a marmoset species At about the same time the virus was obtained also from *Hæmagogus* mosquitoes caught in the same locality

As jungle yellow fever is contracted in forest environment household infections are rare unless the house is within the jungle or close to it The per ons infected are mostly the active adult males who enter the jungle to work Consequently the distribution of infected persons is very different from that in yellow fever outbreaks in which the aegypti mosquito is involved Most women and young children escape jungle yellow fever probably because they seldom visit the forest and because infection is not transmitted from the sick to the well in the home in the absence of any insect vector

Jungle yellow fever may be epidemic as well as endemic From 1934 to 1938 jungle yellow fever spread as an epidemic wave in Brazil progressing steadily in the warmer seasons from Coronel Ponce near the center of the State of Mato Grosso in a southeasterly direction through the States of Goiaz, Minas Gerais and Sao Paulo and into the State of Rio de Janeiro As the city of Rio de Janeiro was under thorough aegypti control it was non infectible and therefore not in danger of an epidemic of yellow fever although a few cases actually were introduced into the city

Etiology

The causative agent of yellow fever is a filtrable virus the properties of which have been studied extensively Its diameter, as determined by filtration through graded collodion membranes, lies between 17 and 25 millimicrons With respect to virulence and pathogenicity it possesses two distinct properties viscerotropism and neurotropism which can be varied independently When both are present as in nature the virus is spoken of as ' pantropic ' If a pantropic strain is passed through a series of mice by intracerebral inoculation, it almost entirely loses its viscerotropism or power to attack the abdominal and thoracic organs especially the liver heart and lungs, for these organs are completely resistant in the mouse while the brain is susceptible At the same time the neurotropism rises After prolonged passage in tissue culture a highly virulent pantropic strain lost most of both its neurotropism and its viscerotropism without losing its antigenic ty or power to produce protective antibodies and immunity

The rhesus monkey the European hedgehog and the mouse are among the best known susceptible animals Other Asiatic monkeys and some of the South American monkeys also are highly susceptible The mouse is susceptible only to the neurotropic component of the virus while the others are susceptible to both If rhesus monkeys are injected intracerebrally with a highly neurotropic virus, they will develop encephalitis If injected in the same way with a pantropic virus they will develop yellow fever with lesions in the liver, kidneys and heart, unless enough immune serum is injected intraperitoneally to protect those organs In that case encephalitis will develop Many animals, e g the white rat, are resistant to both neurotropic and viscerotropic virus Practically all warm blooded animals tested have some power to produce specific protective antibodies after virus injections The serums of some ruminants not infrequently give non specific or false positive results on protection test

Pathology

Gross Pathology —The body of a yellow fever victim after death usually is of a striking yellow color which appears more intense than during life There may be stains of dark vomitus about the mouth or nose Occasionally there are petechiæ or ecchymoses in the skin The *liver* is yellow, either a reddish or brownish yellow or, if very pale and bloodless, a color describable as boxwood chamois or cream The cut surface is of a deep brownish yellow suggesting mustard The size of the liver is about normal The *stomach* usually has fluid contents with which are mixed varying amounts of brownish black, altered blood often divided into flecks or shreds Usually there are petechiæ in the stomach

wall and duodenum The *intestines* may contain altered blood The *spleen* is almost normal in size and appearance The *kidneys* are swollen and pale On section the cortex is pale and has a yellow tinge The *heart* is somewhat pale and flabby and there may be hemorrhages on the cardiac surfaces The *lungs* often are congested, and they are apt to show hemorrhages at the surfaces and sometimes deep in the tissues Other organs show only minor changes

Microscopical Pathology — The lesions in the liver are most striking and characteristic There is profound necrosis and fatty degeneration In mild cases the necrosis involves chiefly the mid zone of the lobule but in extreme cases almost the whole lobule may be necrotic only a fringe of less affected epithelial cells remaining around the central and portal veins The necrosis of the parenchymatous cells is acidophilic as was first emphasized by Councilman Scattered irregularly among the affected cells are certain ones showing acidophilic coagulative hyaline necrosis The mid zonal distribution of the necrosis in the lobule is of great diagnostic importance and appears to be peculiar to yellow fever as has been brought out by Rocha Lima A few polymorphonuclear leucocytes invade the necrotic area but there are no signs of inflammation The *kidneys* show fatty degeneration cloudy swelling and necrosis in the tubular epithelial cells The *heart* muscle shows fatty degeneration the fat being in fine granules Perivascular hemorrhage is the microscopic lesion most commonly found in the *brain*

Symptomatology

Incubation — The period of incubation in man is ordinarily between three and six days

Course of the Disease — The onset usually is sudden Sometimes there is a definite chill but oftener not The temperature rises abruptly at the beginning and the pulse rate goes up correspondingly The prostration is greater than one would expect with the height of the fever There is marked headache and backache and the patient is restless and sometimes sleepless The face is congested and may appear swollen and the eyes are injected The first few days of the disease are aptly called the stage of active congestion There may be nausea and vomiting but the vomitus is free from blood at this stage The tongue is red and pointed Epigastric tenderness or distress is a common symptom Jaundice is not visible for the first two or three days A little albumin may be present in the urine on the second day and more on the third There is leucopenia with the lowest leucocyte counts as a rule around the 5th and the 6th days (Berry and Kitchen) After the initial rise of temperature and pulse the pulse rate falls during the stage of congestion more rapidly than would be in proportion to the irregularly downward tendency of the temperature (*Faget's sign*) and the pulse

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of the attack is the increasing albuminuria At least once a day the urine should be tested by adding a few drops of dilute acetic acid and boiling it in a test tube This can be done at the patient s house over a small alcohol lamp The absence of albumin on the first day followed by its appearance on the second day and a rapid increase for several subsequent days until the sediment obtained by boiling stands high in the tube is strongly in favor of the diagnosis of yellow fever In West Africa this method has been found of great value in searching for cases among negroes in their villages In recent years with the help of laboratory tests many cases, most of them mild have been diagnosed in which the albuminuria was absent or slight

The many mild cases that undoubtedly were missed in the past can now be identified by laboratory procedures although it is still necessary to make the immediate preliminary diagnosis from clinical symptoms urine examination and leucocyte count In order that the diagnosis ultimately may be established definitely in important cases the following procedure is suggested A specimen of about 30 c c of blood should be drawn from a vein as early as possible in the first week of the illness and another at least three weeks after onset and the serum from each specimen should be separated with precautions for sterility and sent to a laboratory with facilities for making yellow fever protection tests in mice If the case is one of yellow fever the first specimen should be devoid of protective antibodies or nearly so and the second should contain the antibodies in considerable amount as shown by the survival of the mice used in the test If the first specimen is taken within the first three or four days of the illness the blood may be highly infectious and every precaution should be taken to prevent its touching the skin of any one when it is drawn or during transportation to the laboratory

If susceptible mice are available and the patient is seen in the first three days of illness an attempt may be made to isolate the virus although the double protection test usually is the most practicable diagnostic method Blood should be drawn from a vein and 0 03 c c of the serum obtained from it should be injected intracerebrally into each of six mice The animals should be observed for at least two weeks If any develop symptoms of encephalitis subinoculations should be made into the brains of 6 normal mice and they should be sent immediately to a yellow fever laboratory for observation and identification of the virus When persons are seen late in the disease it is still worth while to take two blood specimens for protection test the first immediately and the second three weeks or longer after onset If the case is yellow fever the second specimen should show antibodies in much greater quantity than the first A completely negative result with a specimen in late convalescence or even months after the attack should be sufficient to rule out the diagnosis of yellow fever A single positive result

sometimes is very slow during the "stage of stasis" The temperature is not, as a rule very high nor does it often have the pronounced remission sometimes described Constipation usually is present

On the third or fourth day the stage of stasis" begins The turgidity of the face diminishes or disappears Jaundice becomes visible in the conjunctivæ and afterward in the skin The gums are swollen and may bleed if pressed lightly through the lips The dorsum of the tongue is coated and later becomes increasingly dry and brown The patient may feel better Often he vomits a clear fluid mixed with dark brown flakes of altered blood which settle out to form a sediment described as resembling "fly wings", if small in amount, or "coffee grounds if more abundant In severe cases the temperature may fall below normal and the amount of urine may be greatly diminished or almost suppressed The amount of albumin in the urine rises ordinarily for several days after the beginning of the stage of stasis and may reach 5 or 6 gm per liter The urine is deeply colored and the sediment late in the disease contains bile stained epithelial cells and granular casts Petechiæ may appear in the skin, and hemorrhages take place from the mucous membranes The mind is dull, confused and often apathetic There may be marked dilation of the heart and low blood pressure as evidence of myocardial derangement In severe cases there may be hiccough copious vomiting of black material black stools and toward the end coma or convulsions In fatal cases death takes place usually between the sixth and ninth days If recovery takes place the convalescence usually begins between one and two weeks after the onset and progresses steadily toward complete recovery The albumin in the urine decreases and disappears entirely The jaundice persists for a time and gradually fades Asthenia probably related to the changes in the heart muscle may delay convalescence As a rule there are no sequelæ and the patient regains his strength rapidly Relapses and second attacks are practically unknown There is a lifelong immunity after an attack

DIAGNOSIS

A sudden fever with headache and backache prostration nausea and epigastric discomfort and tenderness will raise a suspicion that yellow fever is present but it may be several days before a certain diagnosis is possible Yellow fever occurs most commonly in countries in which malaria is prevalent, and this disease and relapsing fever should be excluded by blood examination The presence of malarial parasites so commonly found in the blood of tropical residents, does not, however, rule out yellow fever If the leucocyte count is low, it helps rule out infections characterized by a high count

Perhaps the symptom most helpful to the diagnostician in the first few days

laxative or mild purgative should be given at the beginning Later a daily enema may be needed Food should be withheld during the acute illness for at least three days except that large quantities of citrus fruit juice may be given throughout the disease and lactose may be added to augment the sugar content If vomiting interferes with oral administration of fluids glucose may be administered intravenously in buffered solution and normal salt solution may be given by hypodermoclysis and tap water by proctoclysis (Berry and Kitchen) If glucose is given 50 gm in 1000 c c of physiological salt solution may be administered three times daily accompanied by thiamine hydrochloride 2 mgm ascorbic acid 50 mgm and nicotine acid amide 15 mgm These vitamins may be given in the glucose solution or separately by mouth or parenterally To combat the acidosis alkaline water should be given freely but in small frequent draughts Bicarbonate of soda may be added to ordinary drinking water when Vichy or other alkaline mineral waters are not available The citrus fruit juices themselves have a high alkalinizing value To relieve vomiting cracked ice and cocaine hydrochloride 0 016 gm (gr ¼) may be given by mouth and codeine sulfate 0 032 gm (gr ½) by hypodermic injection After three to seven days the patient s condition usually will permit the gradual giving of light foods According to Carter it is best not to begin with milk and he suggests rice water chicken soup the crumbled yolk of hard boiled egg etc If the temperature is high an ice cap and cool sponging may give relief Ordinarily the temperature is not very high after the first day or two The mouth should be cleansed frequently

Most important of all is the nursing care The patient should be moved as little as possible and should have complete rest in bed in a quiet airy room Any exertion on his part is especially to be avoided The heart should be watched

PREVENTION

Protection of the Individual — All persons who expect to travel or reside in a region in which exposure to yellow fever is possible should be vaccinated against the disease It is especially important that laboratory and field investigators of yellow fever should be immunized before exposure The vaccine now in wide use has been developed in several stages, and in its several forms has been applied successfully to man since May 1931 Until 1935 the method of Sawyer Kitchen and Lloyd was followed Enough immune human serum to give a passive immunity was injected under the skin and then a single subcutaneous injection of living yellow fever virus modified by long passage through mice was given The use of this vaccine immediately terminated the series of accidental infections in the yellow fever laboratory workers of the International Health Division of

would be strong evidence in favor of yellow fever where there was little chance that the patient could have been exposed to the infection under investigation at any time previously Ordinarily it is wise to establish contact with the labora tory before proceeding with the tests and to arrange for cooperation and advice as relatively few laboratories have the virus, experimental animals and immu nized staff necessary for tests

In advanced severe cases diagnosis from the symptoms usually is easy Black vomit extreme albuminuria and jaundice are outstanding symptoms rarely found together in any other disease Post mortem tissues from yellow fever cases usu ally furnish sufficient evidence for a definite diagnosis At necropsy small pieces of liver spleen kidney and heart muscle should be placed in 10 per cent formalin and sent to the pathologist When a thorough necropsy is not practicable, an adequate specimen of liver may be obtained from the cadaver by the use of the viscerotome when one is available

Prognosis

The mortality varies greatly between epidemics It may be as low as 10 to 20 per cent as reported in some epidemics in America and among African negroes or as high as 70 per cent as observed in white persons in parts of West Africa In the Rio de Janeiro epidemic in 1928 to 1929 the case mortality was 59 per cent As these percentages were based on cases which could be diagnosed from symp toms it is probable that the observed mortality would have been lower if the present methods of laboratory diagnosis had been available

The prognosis should be guarded especially in epidemics with a high mor tality Patients sometimes seem to be holding their own a day or two before a fatal termination In negroes the mortality is relatively low, probably below 20 per cent in West Africa Unless an individual can have more than one attack which seems highly improbable this would suggest a racial partial immunity

Where the symptoms are mild the prognosis is favorable but hiccough copi ous black vomit melena and suppression of urine are symptoms justifying a grave prognosis

Treatment

There is no specific treatment Serum from recovered patients has been shown to have no effect on the course of the disease if given after symptoms have appeared although the serum protects when given to experimental animals before or with the inoculation of the virus The treatment is therefore symptomatic The headache and discomfort of the first few days usually require relief, and a

nevertheless may take certain steps to protect himself and his family in an endemic or epidemic area Care should be taken to avoid places known to be infected He should make sure also that there is no mosquito breeding on or near his premises and that his house is free from mosquitoes and thoroughly protected by wire screening with 18 meshes to the inch Physicians and health authorities should see that all yellow fever patients are protected completely against mosquitoes particularly during the first three or four days of the disease when the blood is infective In emergencies bed nets should be used until the room can be protected with metal screening A bed net in addition would be a valuable precaution during the first four days of illness in a region where the mosquito vector is present If there are adult mosquitoes on the premises in which there is or has been a yellow fever patient the mosquitoes should be killed with an efficient insecticidal spray

Protection of the Community —The attack of the authorities against yellow fever in a city should center in an anti larval campaign to prevent breeding of the mosquito vector *Aedes aegypti* The isolation of individuals under mosquito bars and the destruction of adult mosquitoes should be done by persons other than those in charge of the major operations The anti larval campaign of a city should be under a single competent head The area should be divided into districts or zones if the city is large and the work so organized that every house or apartment is inspected thoroughly every week The inspectors should carry electric flashlights so that they can see into water jars and tanks Tanks and jars should be emptied or sealed so that mosquitoes cannot enter or emerge or stocked with fish or oiled In recent years the tendency has been to use fish only for certain large tanks or cisterns and to depend chiefly on sealing of tanks and the oiling of all containers found to be infected If a sufficient piped water supply is available the number of water containers in use should be diminished as rapidly as possible If there is no such supply every effort should be made to induce the community to get one During an epidemic the mosquito prevalence should be rapidly reduced to a level insufficient to keep yellow fever going Under ordinary conditions a city should free itself of yellow fever in a few weeks and remain non infectible if its house index for larvæ is brought below one and kept there This index is the per cent of the houses and apartments in which mosquito larvæ can be found by thorough inspection The methods used by the Brazilian Yellow Fever Service under Soper in which the application of a mixture of fuel and diesel oil to the water in vessels found to contain larvæ is stressed have made it practicable to keep the aegypti indices close to the vanishing point and frequently at zero Treating containers with oil necessitates thorough scrubbing and resultant removal of adherent aegypti ova before they are refilled Emphasis is placed in Brazil on the occasional search for adult aegypti as a check on

the Rockefeller Foundation, but the difficulty of obtaining sufficient human im mune serum made it impossible to vaccinate large numbers of persons After various intermediate stages, in which further modified virus was used with immune animal or human serum a strain of virus of greatly diminished viscero tropic and neurotropic virulence was evolved from the highly virulent pantropic Asibi strain through prolonged passage through tissue culture by Lloyd Theiler and Ricci and Theiler and Smith This modified strain, known as ' 17D ', was found to be safe for subcutaneous injection without accompanying serum More over it could be maintained indefinitely and multiplied in tissue culture in the presence of the tissues of chick embryos but it was found advisable to increase the virus content of the vaccine by a single final passage in living chick embryo within the egg The embryos are ground with added water, tested for sterility effect on animals and virus content and later centrifuged and dried in the frozen state under vacuum in ampules which are sealed with a blast lamp Each finished lot is tested for bacterial sterility virulence, quantity of virus and also for neuro-tropic virulence by intracerebral inoculation of a rhesus monkey In vaccinating man a single subcutaneous injection of 0 5 c c of the rehydrated and diluted vac cine is given at the insertion of the deltoid of either arm There is no noticeable reaction at the site of injection but there is often a slight or moderate rise of tem perature on the sixth or seventh day, sometimes with headache and general aching Protective antibodies appear in the blood in demonstrable quantity between th seventh and twenty first day The duration of immunity has been fixed for quar antine purposes as extending from 10 days to 4 years after vaccination This seems to be a conservative estimate of the period of immunity based on field and laboratory observations

As originally prepared the 17D vaccine contained a very small amount of normal human serum but this was omitted after the observation in 1942 that a few lots of the vaccine produced numerous cases of jaundice resembling ordinary infective hepatitis after an incubation period of from two to five months Simi lar occurrences after injections of measles and mumps convalescent sera and sub sequent experiments strongly supported the hypothesis that the blood of certain supposedly normal human donors contains an unknown filterable virus capable of causing disea e in man and occasionally circulating subsequently in his blood during a prolonged carrier state Since the serum was eliminated by a change in the method of manufacture jaundice has ceased to appear as the result of yel low fever vaccination

It has not been possible so far to transfer infection from vaccinated men or monkeys to monkeys by means of the bites of *Aëdes aegypti* and it is believed that the risk of such transfer can be ignored

If vaccination has not been available or has been neglected, the individual

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the antilarval work and a guide to the discovery of unusual breeding places which otherwise would be missed When the city has been made non infectible the health organization should work out a plan to keep it so as a part of the regular health work Ships and airplanes from possibly infected ports should be sprayed to kill mosquitoes if any are present, according to the methods required by the quarantine authorities

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Introduction

Definition — Malaria is the name applied to a group of specific infectious fevers caused by several species of animal parasites belonging to the Protozoa which live in and upon the red blood corpuscles of man which they destroy These fevers are characterized by marked periodicity and occur endemically and epidemically in regions where the transmitting agents certain species of Anopheles mosquitoes are present

Historical

The development of our knowledge of malaria has been one of the most interesting and valuable chapters in the history of Medicine but it can be only very briefly considered in this contribution

The malarial fevers were known as clinical entities very early in the history of mankind there being evidence upon some of the temple ruins at Denderah that the ancient Egyptians were acquainted with these infections and in the fifth century B C Hippocrates[1] gave a clear description of these fevers distinguishing them from other continued fevers and dividing them into tertian quartan quotidian and semi tertian However while the Roman physicians and those of the Middle Ages were well acquainted with the various types of malaria it was quite impossible to distinguish them from other acute fevers until after the introduction of cinchona bark into Europe in 1640 The observation that decoctions of this bark caused the symptoms of malaria to disappear rapidly after its administration enabled physicians to roughly differentiate such fevers from other infections but it was not until the discovery of the plasmodia causing malaria by Laveran in 1880 that such differentiation was rendered accurate The method of transmission of the malaria infections by mosquitoes was demonstrated by Ross[2] in 1898 who discovered the cycle of development of the plasmodia in anopheline mosquitoes In 1912 Bass and Johns were first successful in cultivating the three common species of malaria plasmodia upon special culture media and in 1922 Stephens described what he regarded as a new species of plasmodium and named it *Plasmodium ovale* but this species had been previously described by the writer[1] in 1900 who regarded it as a subspecies or variety of *Plasmodium vivax* the tertian malaria plasmodium In 1933 Huff and Bloom[34] described a non pigmented schizogonic cycle of development of certain of the plasmodia of bird occurring within the monocytes and reticuloendothelial cells of the spleen liver and kidneys and their observations have been confirmed since by numerous other observers That a similar cycle of development occurs in the plasmodia causing human malaria apparently has been demonstrated by Raffaele (1937) Casini (1939) Brug (1940) Kikuth and Mudrow (1941) Garcia and others These observations are of fundamental importance in the classification

Egypt the Nile delta Tripoli and Tunis are badly infected and pernicious types are common

Malaria is present in Borneo the Celebes the Moluccas the eastern islands of the Dutch East Indies New Guinea Northern Australia New Britain New Ireland New Georgia the Solomon Islands and the New Hebrides but New Zealand New Caledonia and practically all of the groups of islands in the Central and South Pacific are free from malaria Our troops serving in the Solomons suffered terribly from malaria during World War II but were free from these infections when serving in the islands of the Central and South Pacific

The geographical distribution of the various species of plasmodia is important from an epidemiological standpoint *Plasmodium vivax* the cause of vivax malaria is present in all malarial localities and this is perhaps true of *Plasmodium malariae* the cause of quartan malaria although this species is comparatively rare in most regions *Plasmodium falciparum* the cause of estivo-autumnal malaria, is found only in the warmer regions and is especially prevalent in the tropics where infections with it usually are more numerous than with any of the other species of malaria plasmodia *Plasmodium ovale* the cause of ovale malaria has a limited distribution so far as is known cases of infection with it having been found only in the Philippines New Guinea Russia Persia Palestine, India, China Mauritius South America and East Africa

Etiology

Our knowledge of the morphology and life history of the parasites causing malarial infections has been the growth of many years and to Laveran[5] Richard[6] Marchiafava[7] Bignami[8] Golgi[9] Celli[10] Ross[3] Thayer and Hewettson[11] and many others we owe our now very complete knowledge of these parasites It is now established beyond doubt that malarial infections are caused by certain species of animal parasites belonging to the Protozoa which reach the blood of man through the bites of certain mosquitoes belonging to the genus Anopheles After reaching the blood of man these parasites live upon and within the red blood corpuscles where they undergo a life cycle ending in reproduction or segmentation with the subsequent infection of healthy erythrocytes by the segments or *merozoites* As the segmentation of the parasites occurs at quite regular intervals and as toxic material liberated at the time of segmentation produces the symptoms of the malarial paroxysm the attacks of fever are periodical and constitute the most striking and characteristic clinical feature of malarial infection

Classification of Malaria Plasmodia

The malaria parasites are animal organisms belonging to the Protozoa class Sporozoa All of the parasites causing disease in man are placed in the order

of the malaria plasmodia and profoundly alter our conceptions of the development and life cycle of the plasmodia of malaria in man

The development of the complement fixation reaction as a diagnostic measure in malaria by Coggeshall and Eaton (1938)[15] has demonstrated that antibodies occur in the blood as a result of malarial infection, while the introduction of atabrine (quinacrine) by Mauss and Mietzch in 1933 furnished us with a powerful drug for the treatment of malaria which has proven of inestimable value during World War II, when the supply of quinine was so greatly diminished

Geographical Distribution

The malarial fevers are of nearly world wide distribution, but they are especially frequent and fatal in the tropics and sub tropics

In North America malaria rarely occurs above the forty fifth parallel and is almost unknown in Canada Mild tertian malaria occurs in the New England States and in the Middle Atlantic States, but in the Southern States malarial infections are common and pernicious forms occur especially in the Gulf States Along the Mississippi and Ohio rivers these fevers are frequently met with, and they occur in many of the states of the Middle West In California pernicious types of malaria occur in some of the river valleys The coastal region of Mexico is the home of fatal types of malaria and it may be said that the entire coastal region of Central America is a hot bed of the disease

In South America malaria is a common disease of the coastal region of Colombia, Venezuela, the Guianas, Brazil, Chili, Peru and Ecuador and it is also frequently encountered in the interior, even in the mountain regions

In Europe the northern countries including England, are practically free from malaria In Germany these fevers occur in certain parts of Prussia along the Rhine, and in the swamps of Westphalia and Hannover In France malaria occurs along the Loire and Rhone and in Spain the valleys of the Tago and the Guadalquiver are infected In Italy Greece, Crete Sicily and Turkey malaria is widespread and pernicious types are common In Russia the valleys of the Dneister Dneiper and the Volga are infected as well as the shores of the Black and Caspian seas

In India Ceylon Arabia China and Asia Minor malaria is widely prevalent, and every river valley in Asia may be said to be a home of the disease In Japan the milder types occur but in the Philippine Islands the infection is widespread and pernicious forms occur in most of the islands, especially Luzon, Samar, Mindoro and Mindanao

Africa has always been noted for the severity of the malarial fevers which occur especially along the east and west coast regions The valleys of the Congo Niger and Senegal rivers, the jungle country around the great lakes and lower

Haemosporidia, and the genus, Plasmodium The following species producing disease in man are generally accepted by protozoologists *Plasmodium vivax* the cause of vivax or tertian malarial fever, *Plasmodium malariae* the cause of malariae or quartan malarial fever and *Plasmodium falciparum*, the cause of falciparum or estivo autumnal malaria, and *Plasmodium ovale*, causing a fever with tertian periodicity

Many students of malaria including the writer, consider that at least two species of plasmodia are concerned in the causation of estivo autumnal or sub tertian malaria one producing an infection having paroxysms occurring every forty-eight hours while the other produces an infection with quotidian paroxysms The first type is due to *Plasmodium falciparum*, while the second is caused by a sub species of *Plasmodium falciparum*, which the writer[12] named in 1909 *Plasmodium falciparum quotidianum*

Other species of malaria plasmodia have been described by various observers as *Plasmodium tenue* described by Stephens[15] in 1914, *Plasmodium vivax* var *minutum* by Ahmed Emin[14] in 1914 *Plasmodium perniciosum* by Ziemann in 1915[36] *Plasmodium falciparum* var *aethiopicum* by Raffaele and Lega in 1937[37] and *Plasmodium wilsoni* by Roberts[38] in 1940

While further study may show that some of these are not true species it is probable that a careful study will demonstrate that some are valid, for it is true that minute detailed studies of the morphology of the malaria plasmodia have been greatly neglected by malariologists in general, and a most striking example of this is the recent confirmation by Garcia (1941)[39] that *Plasmodium ovale* is prevalent in certain regions in the Philippine Islands, notably Luzon although the writer described it as occurring there in 1900 forty one years previous to Garcia s confirmation of its presence During this time many eminent malariologists have studied malaria in Luzon and all have overlooked this plasmodium, because of its morphological resemblance to *Plasmodium vivax*

Life Cycle of the Malaria Plasmodia

The malaria Plasmodia have an asexual and a sexual cycle of development The first is passed in the blood of man and the second in certain species of mosquitoes belonging to the Anophelinae The endogenous or asexual cycle passed in the vertebrate host includes repeated asexual reproduction known as *schizogony* and the development of the sexual forms while the exogenous cycle passed in appropriate species of mosquitoes consists of the union of the sexual forms and the development of numerous sporozoites called *sporogony*

Life Cycle in Man — Following inoculation of the sporozoites by the mosquito the red blood cells are invaded by the parasites which in this early stage are known as *trophozoites* The trophozoites enlarge and their chromatin divides, at

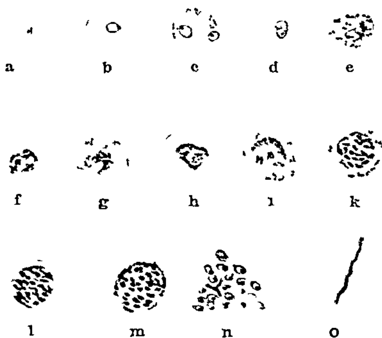


Fig I

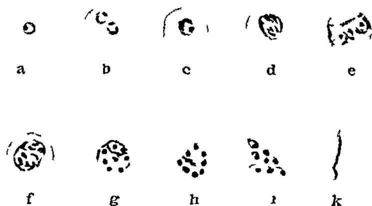


Fig II

Figs 1 and 2 For legends see opposite page

Fig 1 — *Plasmodium vivax* (tertian plasmodium) Stained with Wright's stain

a b c Ring forms of *Plasmodium vivax* Note eosinophilic granules in cytoplasm of erythrocyte in c

d Young gamete

e f g h i Pigmented schizonts of *Plasmodium vivax*

k l m Pre sporulating and sporulating schizonts of *Plasmodium vivax*

n Free spores or merozoites of *Plasmodium vivax*

o Free flagella or microgamete of *Plasmodium vivax*

Fig 2 — *Plasmodium malariae* (quartan plasmodium) Stained with Wright s stain

a b Ring forms of *Plasmodium malariae*

c d Young gametes

e So called band form of schizont of *Plasmodium malariae*

f g h Pre sporulating and sporulating schizonts of *Plasmodium malariae*

i Free spores or merozoites of *Plasmodium malariae*

k Microgamete of *Plasmodium malariae*

Facing Figs 1 and 2

which time they are called *schizonts* These enlarge and finally divide into several small bodies known as *merozoites* which are liberated into the blood stream and invade other red blood corpuscles after which they become trophozoites and renew the process of schizogony

The time consumed in schizogony differs with each species of plasmodium it is approximately 48 hours in *P vivax* and *P ovale* 72 hours in *P malariae* and between 36 and 48 hours in *P falciparum*

Exo-erythrocytic Cycle in Man —Following the observations of Huff and Bloom Raffaele James and Tate Kikuth and Mudrow and others in which a non pigmented cycle of development of several species of malaria plasmodia occurring in birds was proven to occur a similar cycle of development apparently has been demonstrated in man for the species of plasmodia producing malaria in this host The exact method of such development has not been determined accurately to date but it has been demonstrated that non pigmented forms of the plasmodia invade and develop in the monocytes and reticuloendothelial cells of the internal organs and the bone marrow appearing as rounded bodies containing masses of chromatin but devoid of pigment These bodies finally divide into smaller bodies which may enter the red blood corpuscles and become schizonts developing pigment as usual The length of this cycle of development still is undetermined but its occurrence apparently is most important in the evolution of the plasmodia and probably explains the periods of latency in which no parasite can be found in the peripheral blood while it also offers an explanation of the occurrence of relapses in malarial infections

Life Cycle in the Mosquito —Among the merozoites liberated at the time of schizogony in the blood of the human host are bodies that have become differentiated into male and female forms which are known as *gametocytes* Unless these forms are taken up by appropriate mosquitoes they undergo no further development in man but in the mosquito they undergo a definite cycle of development The male forms are known as *microgametocytes* and the female forms as *macrogametocytes* When blood containing gametocytes reaches the stomach or mid gut of the mosquito the microgametocytes throw out long motile filaments which finally are liberated These are known as *microgametes* and eventually one of these penetrates the female cell which has undergone certain maturation changes and is now known as a *macrogamete* and fertilizes this cell The resulting body is called a *zygote* and the process of fertilization occurs in the mid gut of the mosquito

The zygote now elongates and becomes motile and is known as an *ookinete* It penetrates the lining membrane of the mid gut and comes to rest between that layer and the elastic membrane where it becomes spherical in shape and forms a cyst which is called the *oocyst* and within this cyst there are developed multitudes of long slender spindle shaped bodies the *sporozoites* The sporozoites

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are liberated in the hemal cavity or hemocele by the rupture of the cyst and may be found later in all of the tissues of the mosquito but especially in the cells of the salivary glands and ducts When the infected mosquito bites man the salivary secretion containing the sporozoites is injected into the puncture wound, and the sporozoites after further development, apparently in the monocytes and reticulo endothelial cells reach the blood invade the red blood corpuscles and become trophozoites thus initiating the human or asexual phase of the life cycle of the plasmodia

The sexual cycle of development within the mosquito usually is completed in from ten to fourteen days differing in different species of mosquitoes and with different species of the plasmodia as well as with conditions of temperature and humidity and so far as known can only be completed in mosquitoes be longing to the genus *Anopheles*

Morphology of the Malaria Plasmodia

In attempting to describe the morphology of the malaria plasmodia it is necessary to describe their structure during different stages of development in man and in the transmitting mosquito These parasites have two distinct life cycles the one in man being known as schizogony or the asexual cycle while that in the transmitting mosquito is known as sporogony or the sexual cycle The various developmental forms of the plasmodia, occurring in the two hosts vary widely in morphology so that it is necessary to consider the forms in each cycle of development separately

Morphology of Malaria Plasmodia in Man

In describing the morphology of the various malaria plasmodia in man each species will be described separately

Plasmodium vivax (The Tertian Parasite) (Figs 1 6 7 8 9 and 10) —The parasite of tertian fever completes its human cycle in the red blood corpuscles of man in forty eight hours thus causing a febrile paroxysm every other day In fresh specimens of blood which have not been stained, the parasite appears at first within or on the red blood corpuscle as a dim, hyaline spot of irregular outline known as the *tropho oite* As development occurs ameboid motility be comes active and fine grains of pigment of a reddish brown color develop At this stage in its growth it is known as a *schi ont* At the end of twenty four hours the parasite fills about half of the infected red corpuscle which is con siderably enlarged the pigment has increased in amount and there is active ameboid motility From this time on the plasmodium enlarges rapidly and at the end of forty hours fills the entire red cell The pigment tends to collect in one or more masses at or near the center of the parasite, and at the end of forty

Fig 3 — *Plasmodium falciparum* (estivo autumnal sub tertian plasmodium) Stained with Wright s stain

a b c d Ring forms of schizont of *Plasmodium falciparum*

e f g Pigmented schizonts of *Plasmodium falciparum*

h i k Pre sporulating and sporulating schizonts of *Plasmodium falciparum*

l Crescentic female gamete or macrogametocyte Note slender shape

m Crescentic male gamete or microgametocyte Note plump shape

Fig 4 — *Plasmodium falciparum quotidianum* (quotidian estivo autumnal plasmodium)

a b c d e Ring forms of *Plasmodium falciparum quotidianum* Note very minute size as compared with the same forms of *Plasmodium falciparum*

f g Pigmented schizonts of *Plasmodium falciparum quotidianum*

h i k Pre sporulating and sporulating forms of *Plasmodium falciparum quotidianum* Note minute size of spores or merozoites

l Crescentic female gamete or macrogametocyte of *Plasmodium falciparum quotidianum* Note slender form

m Crescentic male gamete or microgametocyte of *Plasmodium falciparum quotidianum*

Fig 5 — A a Young male gamete of *Plasmodium vivax* or microgametocyte

b Nearly fully developed microgametocyte of *Plasmodium vivax* Note light blue staining of cytoplasm

c Young female gamete or macrogametocyte of *Plasmodium vivax*

d Fully developed macrogametocyte of *Plasmodium vivax* Note deeper staining

e Flagellated microgametocyte of *Plasmodium vivax*

B a and b Microgametocytes of *Plasmodium malariae* c and d Macrogametocytes of *Plasmodium malariae*

e Flagellated microgametocyte

Facing Figs 3 4 and 5

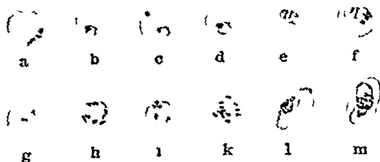


Fig III

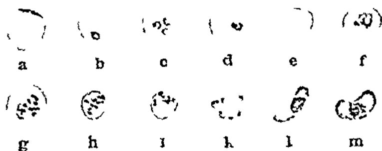


Fig IV

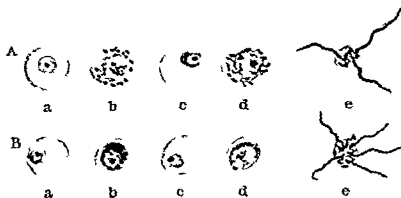


Fig V

Figs 3 4 and 5 For legends see opposite page

eight hours the organism breaks up into from twelve to twenty four segments or *merozoites* These merozoites infect healthy red blood corpuscles and the cycle of the development is repeated

In specimens of blood stained with Wright s or other Romanowsky stain the earliest stage in the development of the tertian parasite is the so-called *ring form* which appears as a delicate blue stained ring of protoplasm at one portion of the periphery of which is a ruby red dot of chromatin the red corpuscle staining a salmon pink color As the parasite enlarges the ring form is lost and it appears as a blue stained body of irregular shape containing several threads or dots of red chromatin and granules of greenish brown pigment The red blood corpuscles containing the plasmodia show numerous pinkish granules in those portions of the cytoplasm not occupied by the parasites these granules being known as Schuffner s dots an appearance very characteristic of tertian infection

A few hours before the time of segmentation the bizarre shape of the plasmodium is lost and it becomes oval or circular in contour In stained preparations it appears as a blue mass of cytoplasm containing numerous large granules and small masses of chromatin which stain a bright red or violet together with greenish brown pigment granules The invaded red blood corpuscle is almost filled by the parasite and is very greatly enlarged As segmentation approaches chromatin granules and masses collect into compact oval or spherical masses throughout the cytoplasm while the pigment granules become collected into an irregular mass near the center of the plasmodium At the time of segmentation the blue stained cytoplasm is differentiated into numerous small oval bodies each containing a chromatin mass stained a bright red or violet The number of these bodies varies from twelve to twenty four as a rule and they are known as *merozoites* After segmentation is completed the young plasmodia or merozoites are frequently observed just entering the red blood corpuscles consisting of an oval or ring shaped blue stained body having a red dot of chromatin at some portion of the periphery or as a slender band of blue stained cytoplasm situated at the edge of the corpuscle having a red dot of chromatin near the center of the band Besides the forms of the tertian malaria plasmodium described other forms develop in the blood of man during the human life cycle which are intended to undergo development in the mosquito These forms are known as *gametocytes* and will be described when the forms developing in the mosquito are considered

Plasmodium malariae (The Quartan Parasite) (Figs 2 11 12 13 14 and 15) — The quartan malaria plasmodium completes its cycle of development in man in approximately seventy two hours causing the form of malaria characterized by a febrile paroxysm upon every fourth day

In unstained preparations the plasmodium is first to be distinguished in the infected red blood corpuscle as a minute hyaline ovoid or ring like body Ame

boid motility is less pronounced than in the tertian parasite, and the parasite is smaller at every stage of its development Pigment is formed within a few hours but it is smaller in amount and in the form of larger grains than in the tertian parasite and is less actively motile The plasmodium gradually enlarges until at the end of seventy two hours it fills the red blood corpuscle, but unlike the tertian organism the pigment is much less in amount and ameboid motility is lost many hours before segmentation The infected red corpuscle does not show Schuffner s granules and at no time is it enlarged, as in infection with the tertian plasmodium

At the time of segmentation the pigment becomes collected in one large mass at or near the center of the parasite and faint striations become visible in the cytoplasm dividing the plasmodium into from six to twelve segments, making the entire organism resemble a daisy These segments, or *merozoites* are finally liberated the pigment becomes free in the blood plasma and the process is repeated by the invasion of new corpuscles by the merozoites

Similar staining reactions with the Wright stain occur in this species as in *Plasmodium vivax* although the cytoplasm of this species usually stains a more brilliant blue and Schuffner s granules are not present in the cytoplasm of the invaded red blood corpuscles The general appearance of the plasmodium during its growth is similar to that in stained preparations of *Plasmodium vivax* but the organism is always regular in contour and the bizarre shaped organisms so common in infections with the tertian plasmodium, are never noted in this type of infection

In stained preparations of *Plasmodium malariae* the so called ' band forms' are frequently observed consisting of a band of blue stained cytoplasm containing pigment and red chromatin granules, stretching directly across the infected red blood corpuscle This form is very rarely observed in tertian infections but is quite characteristic of infections with the quartan plasmodium A feature which serves to distinguish this species from the tertian plasmodium, is the lack of enlargement of the infected erythrocyte which is invariably present in cells invaded by the tertian plasmodium even before the development of pigment The segmenting plasmodia of this species contain from six to twelve oval or round bodies the merozoites each consisting of a blue stained ring of cytoplasm containing a bright red dot of chromatin

Plasmodium falciparum (The Sub tertian Estivo autumnal Parasite) (Figs 3 16 17 18 19 and 20) — This species of malaria plasmodium completes its human life cycle in approximately forty eight hours, but in the opinion of the writer, never in twenty four hours as stated by many authorities It gives rise at the time of segmentation to a type of malarial fever characterized by a very peculiar temperature curve the paroxysms occurring every other day, as in infection with *Plasmodium vivax* the tertian plasmodium

Like the tertian and quartan plasmodia this species as observed in unstained preparations appears first within or upon the red blood corpuscle as a hyaline mass of protoplasm generally ring shaped the parasite resembling a well defined hyaline ring within or upon the invaded red blood corpuscle Multiple infection with such ring forms is very commonly observed in infection with this parasite

The ring forms increase in size, and at the end of from sixteen to twenty hours a small amount of pigment develops in the form of a few reddish brown or nearly black granules After the development of pigment the ring form is lost the plasmodium increases in size becomes more clearly defined and is circular or irregularly oval in shape Ameboid motion is absent or very sluggish and the bizarre shaped plasmodia so characteristic of infection with *Plasmodium vivax* are very rarely observed The writer has observed forms which resemble the description by Stevens of *Plasmodium tenue* in undoubted infections with this species In the usual infection with *Plasmodium falciparum* only the ring forms and the small pigmented forms occur in the peripheral blood and the latter are generally very few in number In infections of pernicious character the larger pigmented forms and the segmenting forms are frequently encountered in the peripheral blood

Just prior to segmentation the *schizonts* of this species fill from two-thirds to three quarters of the infected red blood corpuscle the pigment is collected in a solid mass near the center of the parasite and faint radial striations may be seen dividing the organism into segments Segmentation occurs every forty-eight hours approximately but may be delayed as long as fifty hours or occur as early as forty to forty four hours but it never occurs in twenty four hours as claimed by those who believe in only one species of the estivo-autumnal plasmodium At the time of segmentation the plasmodium fills from three-quarters to almost the entire infected erythrocyte and the segments or *merozoites* number from ten to thirty the average number being between eighteen and twenty four The infected erythrocyte is not enlarged and is often smaller than normal It may be darker green in color than normal and is often crenated

The staining reactions of *Plasmodium falciparum* with Wright's stain are similar to those of the other malaria plasmodia the cytoplasm staining blue the chromatin of the nucleus red while the nutritive vacuole and the achromatic zone remain unstained The youngest ring forms are very frequently observed attached to the periphery of the erythrocyte appearing as slender lengthened threads or spindles of blue stained cytoplasm containing a red chromatin dot either at one end or somewhere along the length of the cytoplasm The ring forms resemble those of the other malaria plasmodia but the rings are thicker and frequently present a much expanded portion usually situated opposite the chromatin dot which represents the nucleus Pigmented ring

forms and larger pigmented forms are often seen in small numbers in stained preparations. The larger pigmented forms occur usually in pernicious infections and present a blue stained cytoplasm in which may be observed a small amount of chromatin while in the pre segmenting plasmodia the chromatin is collected in small irregular red stained clumps within the blue stained cytoplasm. The segmenting forms, in stained preparations almost fill the infected erythrocyte and the segments or *merozoites*, consist of a small blue stained mass of cytoplasm containing a spherical, or oval red stained dot of chromatin.

In stained preparations the infected erythrocytes sometimes show a form of degeneration known as basophilic degeneration characterized by the occurrence in the cytoplasm of bluish stained dots known as "Maurer's dots". The cells are but little smaller than normal, as a rule, although a moderate reduction in size is frequently observed.

Plasmodium falciparum quotidianum (The Quotidian Estivo autumnal Parasite) (Fig 4) — This sub species of *Plasmodium falciparum* resembles the latter organism in general morphology but is much smaller during every stage in its development in the blood of man. In both the living condition and in stained preparations the youngest forms of the *schizont* the so called "ring forms", are very minute and can be easily overlooked or mistaken for artifacts or piroplasmata. In stained preparations the chromatin in the "ring forms" instead of being in the form of a minute red dot or two such dots is collected along the periphery of the "ring" in a granular elongated mass thus forming a considerable portion of the "ring form". The infected red blood cell is generally smaller than normal and much crenated and in unstained preparations dark green or "brassy" in color. The fully grown segmenting plasmodia of this sub species only fill about one half of the infected erythrocyte and the segments or *merozoites* number from six to eighteen the average number being twelve to fourteen. Segmentation occurs approximately every twenty four hours and is never delayed longer than twenty six hours thus differing markedly from *Plasmodium falciparum* in which segmentation occurs approximately every forty-eight hours. Schuffner's dots do not occur in the infected erythrocytes but basophilic degeneration of these cells is observed frequently (Maurer's dots).

Plasmodium Ovale — This now generally recognized species of malaria plasmodium was first described by the writer in 1900[13] and later redescribed and named by Stephens in 1922[31]. More recently James Nicol and Shute[37], Mühlens[33] and many others have studied this species and have demonstrated its specificity.

Plasmodium ovale undergoes its complete asexual development in the erythrocytes of man in a forty-eight hour period segmentation occurring at the end of that time. Morphologically *Plasmodium ovale* resembles *Plasmodium malariae* although the infected blood cell is slightly enlarged while the segmenting forms contain from six to twelve *merozoites* the most common number being

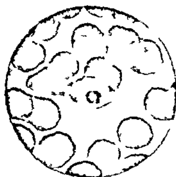


FIG 6 — *Plasmodium vivax* Tertian malaria plasmodium Young *schizont*

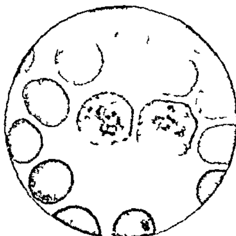


FIG 7 — *Plasmodium vivax* Tertian malaria plasmodium Two young *gametes* *

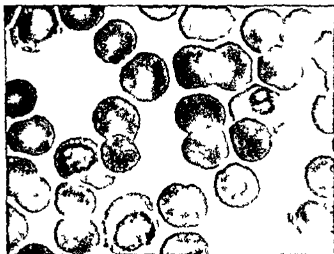


FIG 8 — *Plasmodium vivax* Tertian malaria plasmodium. Half grown *schizonts*

In all of these photo micrographs note the great enlargement of the red blood corpuscles containing the plasmodia a characteristic change in the size of the infected cell in tertian infections

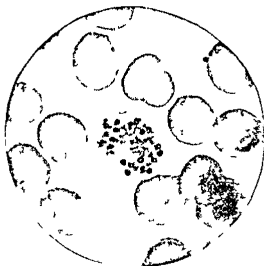


Fig 9—*Plasmodium vivax* Tertian malaria plasmodium Sporulating *schizont* *

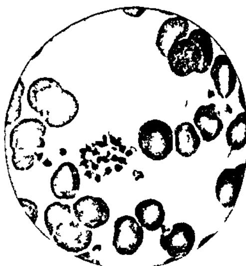


Fig 10—*Plasmodium vivax* Tertian malaria plasmodium Sporulating plasmodium showing free spores or *merozoites*

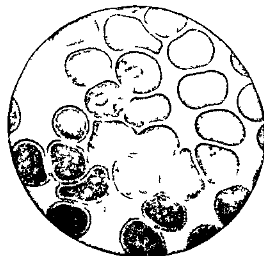


Fig 11—*Plasmodium malariae* Quartan plasmodium Ring form *schizonts*

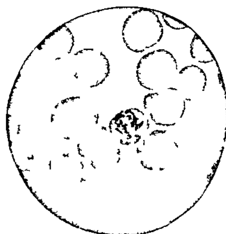


Fig 12—*Plasmodium malariae* Quartan malaria plasmodium Half grown *schizont* a so called band form characteristic of quartan infection

In this photomicrograph note the great enlargement of the red blood corpuscles containing the plasmodia a characteristic change in the size of the infected cell in tertian infections

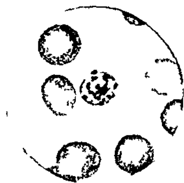


Fig 13.—*Plasmodium malariae* Quartan malaria plasmodium Sporulating *schizont* Not one spore or *merozoite* just about to leave the parent body

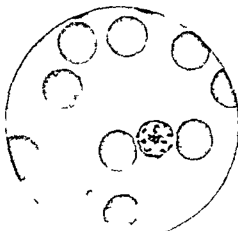


Fig 14.—*Plasmodium malariae* Quartan malaria plasmodium Sporulating *schizont* Note regular arrangement of the *merozoites* and their small number compared with *Plasmodium vivax*

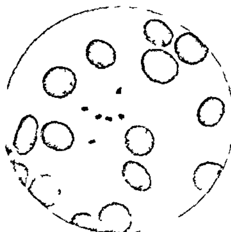


Fig 15.—*Plasmodium malariae* Quartan malaria plasmodium Sporulating *schizont* showing free spores or *merozoites*

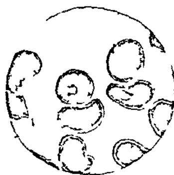


Fig 16.—*Plasmodium falciparum* Subtertian Estivo autumnal plasmodium Ring form *schizonts*

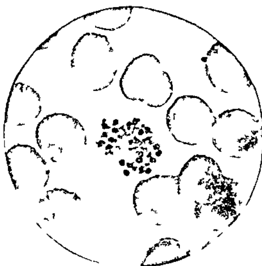


FIG 9 —*Plasmodium vivax* Tertian malaria plasmodium Sporulating *schizont* *

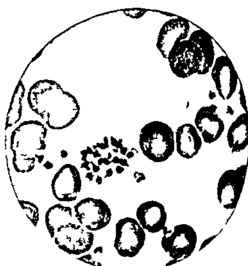


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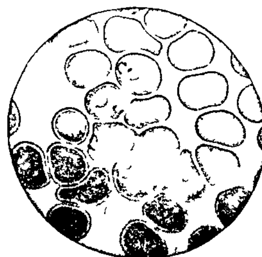


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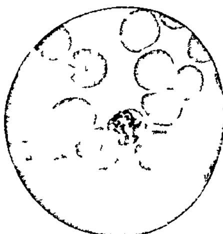


FIG 12 —*Plasmodium malariae* Quartan malaria plasmodium Half grown *schizont* a so called band form characteristic of quartan infection

In this photomicrograph note the great enlargement of the red blood corpuscles containing the plasmodia a characteristic change in the size of the infected cell in tertian infections



FIG 17 —*Plasmodium falciparum* Subtertian Estivo autumnal plasmodium Sporulating *schi nt* Note that sporulation is completed before the infected erythrocyte is entirely d troyed the sporulating plasmodium filling but a little over one half of the infected red cell



FIG. 18 —*Plasmodium falciparum* Sub-tertian Estivo autumnal plasmodium Large phagocyte containing much malarial pigment and a sporulating form of *Plasmodium falciparum*

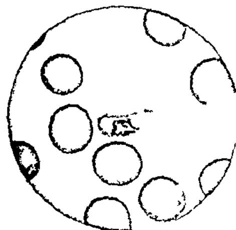


FIG 19 —*Plasmodium falciparum* Subtertian Estivo-autumnal pla mod um Male *gamete* or *n icrog imetocyte* Note crescentic form an l plump appearance of the crescent

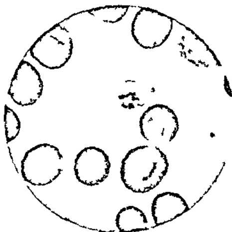


FIG 20 —*Plasmodium falciparum* Subtertian Estivo autumnal plas nodium Female *gamete* or *n acrogametocyte* Note slender form of the crescent

eight The infected red blood cell often is oval in shape hence the name *P ovale* which refers to the shape of the infected cell rather than to that of the plasmodium

The periphery of the infected cells generally shows a ragged appearance, and Schuffner's dots appear early in the development of the parasite, as shown in stained preparations Ameboid activity of this plasmodium, unlike that of *P vivax* is very slight, and the pigment is light brown in color fine in appearance and distributed throughout the cytoplasm of the organism

In *stained* preparations *Plasmodium ovale* presents the same staining reactions as the other malaria plasmodia The *trophozoites* or ring forms' stain a deep blue and the chromatin dot or dots usually are larger than in *P malariae* Cells containing ring forms frequently show Schuffner's dots The *schizonts* resemble those of *P malariae* in stained preparations, usually are round in shape, situated within an oval red blood corpuscle and in the presegmenting forms the chromatin is distributed throughout the cytoplasm of the parasite in irregular, diffuse masses of granules or as irregular deeply stained clumps while the pigment is scattered throughout the organism and has a light greenish brown color The segmenting forms present from six to twelve *merozoites*, irregularly arranged and staining a deep blue each containing a large dot of red or violet chromatin

From this brief description of the morphology of *Plasmodium ovale* it will be noted that it is a plasmodium resembling *P malariae* in morphology but producing in the infected erythrocyte the same changes as does *P vivax* i e, enlargement of the infected cell and the occurrence of Schuffner's dots, although the latter appear much earlier than in infections with *P vivax*

Morphology of the Gametocytes

It has been stated already that during the process of schizogony certain forms of the malaria plasmodia develop in the blood of man, which are intended to undergo further development in the mosquito and that these forms are called gametocytes These are sexual forms the male being known as a microgametocyte and the female as a macrogametocyte Individuals whose blood contains these forms are true carriers of malaria, and their recognition is of the greatest importance in the prophylaxis of these infections

The morphology of the gametocytes can be studied best in stained blood films, the stain employed being either the Wright or Giemsa stain When fully developed, the gametocytes of *Plasmodium vivax P ovale* and *P malariae* are spherical in shape while those of *P falciparum* and *P falciparum quotidianum* are crescentic in shape While in the blood of man segmentation never occurs, nor do they develop further unless taken up by an appropriate mosquito during biting

As the morphology of the gametocytes of *P vivax*, *P ovale* and *P malariae*

is similar one description will answer for all three species The earliest stage of development as observed in preparations stained with Wright s stain consists of a ring of blue stained cytoplasm containing within it a bright red dot of chromatin As these enlarge they retain their round or oval shape and when fully developed fill the infected red blood corpuscle The *microgametocytes* stain a pale blue color and show within them a mass of granules or fine fibrils of red stained chromatin arranged in the form of a spindle or loose skein lying in an unstained area within the pale blue cytoplasm If about to exflagellate the chromatin may be divided into several dark red masses and if flagellating the flagella or *microgametes* stained red may be seen projecting from the periphery of the organism

The *macrogametocytes* stain a much deeper blue than do the *microgametocytes* and the red stained chromatin instead of being arranged in a loose skein appears as a compact red mass near the periphery of the parasite In both pigment occurs that in the microgametocytes being arranged as an irregular mass while in the macrogametocytes it is arranged in minute masses or in a wreath like manner near the periphery of the organism

The gametocytes of *Plasmodium falciparum* and *P falciparum quotidianum* are crescentic instead of round in shape but appear at first within the infected red blood corpuscle as ovoidal or round blue stained bodies having a central dot of red chromatin As development proceeds these bodies become crescentic in shape and when fully developed they are definitely crescentic or lima bean like in shape The *microgametocytes* stain a pinkish blue with the red stained chromatin scattered in fine grains over a portion of the cytoplasm while the pigment occurs as dark brown or black granules throughout the body of the parasite The *macrogametocytes* stain a blue or bluish lavender the deep red chromatin is collected in a compact mass at or near the center and the pigment is dark brown or black in color and occurs in large granules and in minute masses nearer the chromatin sometimes in a wreath like manner surrounding the nucleus

The microgametocytes or male gametocytes are much plumper in appearance than the macrogametocytes or female forms usually being kidney or lima bean like in shape while the macrogametocytes are typically crescentic and often occur as very slender crescents

Development of Gametocytes within the Mosquito

The cycle of development of the gametocytes within the mosquito has been described already on a previous page

THE MOSQUITOES TRANSMITTING THE MALARIA PLASMODIA

As already stated only mosquitoes belonging to the *Anophelinae* are capable of transmitting malaria so far as is known and although many species have been

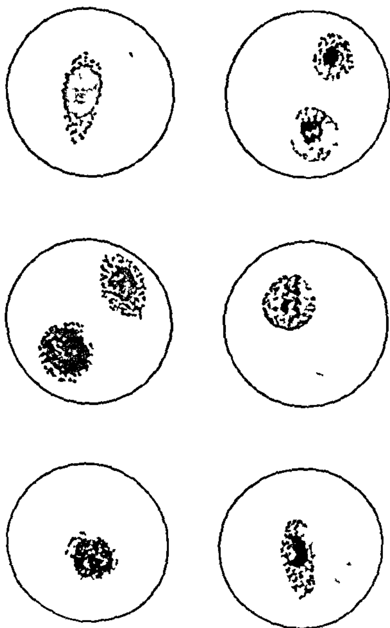


FIG 20 (a) — *Plasmodium ovale* Developmental forms of schizonts of *Plasmodium ovale* Note the oval shape of the infected erythrocyte the presence of Schuffner's granules and the general resemblance in morphology of this plasmodium to *Plasmodium malariæ* the quartan plasmodium × 1000 (after Mühlens)

or syphon The anopheline larvae owing to this are compelled to lie parallel to the surface of the water while other mosquito larvae hang head downward at an acute angle with the surface of the water

The Imago or Adult — Adult mosquitoes belonging to the *Anophelinae* are distinguished by attention to the following points

a *The Relative Length of the Palpi and Proboscis* — In the *Anophelinae* the palpi of the female are as long or longer than the proboscis while in non malaria carrying mosquitoes, the palpi are much shorter than the proboscis

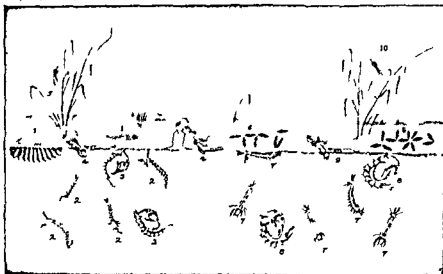


Fig 21 — Illustrating life cycle of culicine and anopheline mosquitoes (*After Ascoli*)
1 Ova of culicine mosquito Note boat like mass
2 Larvae of culicine mosquito Note long breathing tube and position with relation to surface of the water
3 Pupa of culicine mosquito
4 Adult culicine mosquito emerging from pupal case
5 Adult culicine Note position in resting as compared with anopheline mosquito
6 Ova of anopheline mosquito Note separate ova and shape
7 Larvae of anopheline mosquito Note lack of breathing tube and position with relation to the surface of the water
8 Pupa of anopheline mosquito
9 Adult of anopheline emerging from pupal case
10 Adult anopheline Note position in resting as compared with culicine mosquito

b *The Resting Position* — When resting upon a surface the mosquitoes that transmit malaria form a distinct angle with the surface the body and proboscis being in a straight line while other mosquitoes appear hump backed owing to the fact that the abdomen forms a curve with the thorax

c *The Spotted Wings* — Many of the common malaria transmitting mosquitoes have spotted wings This is not confined however to malaria mos

infected experimentally with the plasmodia only a comparatively small number of species have been proven to transmit malaria. The following list gives the most important species which have been found naturally infected or act as natural transmitters of malaria to any great extent. Some of these only become important under certain natural or artificial conditions, or where other more active species are absent.

United States. — *Anopheles quadrimaculatus, A. punctipennis, A. pseudopunctipennis, A. crucians.*

South America. — *Anopheles albimanus, A. argyritarsis, A. braziliensis, A. cruzi, A. intermedius, A. punctipennis, A. pseudopunctipennis, A. bellator, A. darlingi, A. tarsimaculatus, A. oswaldi.*

Panama. — *Anopheles albimanus, A. argyritarsis, A. pseudopunctipennis.*

Europe. — *Anopheles maculipennis, A. plumbeus, A. superpictus, A. elutus.*

Asia. — *Anopheles barbirostris, A. bifurcatus, A. culicifacies, A. elutus, A. fluviatilis, A. funestus, A. fuliginosus, A. hyrcanus, A. jeporiensis, A. ludlowi, A. listoni, A. maculatus, A. maculipalpis, A. minimus, A. pulcherrimus, A. philippinensis, A. sergenti, A. stephensi, A. sinensis, A. subpictus, A. sundiacus, A. umbrosus, A. turkhudi, A. willmori, A. umbrosus, A. varuna.*

Netherlands East Indies. — *Anopheles aconitus, A. barbirostris, A. fuliginosus, A. hyrcanus, A. kochi, A. maculatus, A. leucosphyrus, A. maculatus, A. minimus, A. subpictus, A. sundiacus, A. umbrosus.*

Australia, Solomon Islands, New Hebrides. — *Anopheles annulipes, A. bancrofti, A. punctulatus.*

Philippine Islands. — *Anopheles barbirostris, A. fuliginosus, A. maculatus, A. minimus, A. sundiacus, A. umbrosus.*

Africa. — *Anopheles culicifacies, A. costalis, A. funestus, A. gambiae, A. hancocki, A. hargreavesi, A. moucheti, A. nili, A. pharoensis, A. pretoriensis.*

Differentiation of Mosquitoes Which Transmit Malaria

Careful attention to a few and simple differential points should enable anyone of average intelligence to determine whether mosquitoes belonging to the genus *Anopheles* are present in any locality, and such determination is important for if such mosquitoes are present they may be transmitters of the malaria plasmodia. Having determined the presence of anopheline mosquitoes, collections of the insects should be made and forwarded to a competent entomologist for determination of species, as many species of anopheles do not transmit the malaria plasmodia.

The Ova. — The ova are never found in raft like masses but occur singly, the ends often being connected, thus forming geometrical patterns. They also possess lateral extensions or "floats."

The Larvae. — The larvae are easily distinguished from those of mosquitoes not belonging to the *Anophelinae* by the absence of the long respiratory tube

or syphon The anopheline larvae owing to this are compelled to lie parallel to the surface of the water while other mosquito larvae hang head downward at an acute angle with the surface of the water

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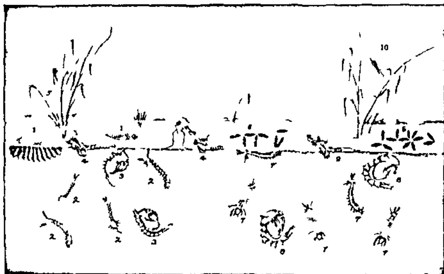


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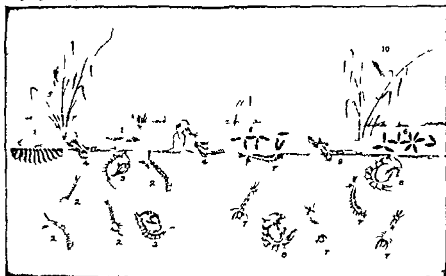


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quitoes but when observed is presumptive evidence that the insect may belong to some species concerned in the transmission of this infection

Cultivation of the Malaria Plasmodia

Bass and Johns[4] were the first to cultivate successfully the malaria plasmodia outside of the human body They used a culture medium composed of blood from the malarial patient to which has been added one tenth c c of a 50 per cent solution of dextrose They have not been able to cultivate the plasmodia through more than four generations as a rule and this fact has prevented the method from being of much use in the study of these parasites Bass and Johns have cultivated *Plasmodium vivax Plasmodium malariae Plasmodium falciparum* and *Plasmodium falciparum quotidianum* in this manner and their work has been confirmed by numerous observers In cultures only the forms concerned in the human life cycle the schizonts undergo any development, and gametocytes if present do not undergo any developmental changes or present any of the phases of development that normally occur in the middle intestine of the mosquito Parthenogenesis does not occur in cultures, nor do resting or resistant forms of the plasmodia develop so far as known

Method of Transmission of Malaria

Until quite recent times it was held by most authorities that the malarial fevers were transmitted either through polluted air or water, but it is now known that these infections are only transmitted through the bites of certain infected mosquitoes in which the malaria plasmodia have gone through a definite cycle of development as has been described in preceding pages Although this is true there are numerous factors that exercise an indirect effect in the transmission of the infection either through favoring the development of the infecting insect or favoring the development of the plasmodia within man Such factors will be considered later but there are some general factors influencing infection which will be considered here

Race — It will sometimes be noted in the literature that observers state that certain races are immune to malaria This is not true, for there is no race of man immune to these infections although some races through repeated infections in early life become largely immune to the poisons produced by the plasmodia and do not show definite symptoms of an infection which may, nevertheless be present as proved by the presence of plasmodia in the blood Thus native races in a badly infested district possess a relative immunity to the infections but this is not a racial characteristic These people, if exposed to infection under conditions which greatly depress their resistance, will develop the symptoms of malaria just as do those who have never lived in a malarial locality

Age — Children are more susceptible to malarial infection than adults although in malarial localities this may be accounted for by the relative immunity the adult population has developed through repeated infections in childhood. The apparent susceptibility of children to malaria also is accounted for partly by the fact that mosquitoes bite children in preference to adults and because children do not notice the biting of the insect as much as adults. Thus there is a much greater chance for infection in children but it is quite doubtful if children are really any more susceptible to malaria than adults if the factors mentioned be considered.

Sex — Men are more frequently infected with malaria than women owing to their being bitten more frequently by mosquitoes because of their occupations.

Occupation — Occupations that depress the general health or that expose the individual to the chance of being bitten by mosquitoes favor the transmission of the disease. Out-door occupations during the time that the malaria-carrying mosquitoes bite greatly favor infection.

Locality — Certain regions are notoriously malarial while in others little or no malaria occurs. These differences are due to local conditions favoring the breeding of the transmitting mosquitoes, the presence of infected individuals or carriers, and other local conditions favoring infection. The type of malaria is also greatly affected by locality, in some regions only the benign tertian infections being present, while in others the most severe and fatal forms of pernicious malaria are prevalent.

Climate — Climate only influences the transmission of malaria as it favors the breeding of the mosquitoes transmitting these infections or the growth of the plasmodia in man. In the tropics the climatic conditions are especially favorable in both regards and in such regions malarial infections are most prevalent and the pernicious types occur most frequently. The effect of the seasons is marked especially in the temperate zone, malaria being most prevalent when the season is most favorable to the breeding and development of the transmitting mosquitoes. Thus in the temperate zones malaria does not occur in the winter but becomes more and more common as the weather grows warmer until it reaches its height, as regards the number of infections, in summer and early autumn. In the tropics malaria is most prevalent just toward the end of the rainy season and least prevalent during the latter portion of the dry season.

Soil, Altitude and Moisture — These factors influence the prevalence of malaria because they influence the breeding and development of the transmitting mosquitoes. It is well known that malaria is most prevalent in low lying marshy regions but if conditions as regards temperature, moisture, the presence of suitable species of mosquitoes and carriers of the plasmodia are favorable malarial infections will occur at high altitudes as well as in lowlands.

Immunity in Malarial Infection

It has been stated already that there is no racial immunity to malaria, but a *natural immunity* to these infections does occur in certain individuals, a fact that is frequently noted in the case of troops operating in a malarial locality or stationed in such a locality In such instances it is often observed that certain individuals escape the infection no matter how long they are exposed while others are repeatedly infected The writer has observed many instances of this kind in soldiers and officers serving in very malarial regions, who never developed malaria although taking no precautions against infection

Acquired immunity to malaria is frequently the result of repeated infections brought about by long residence in malarial localities This type of immunity is most often illustrated in the natives of such localities and generally consists in a relative immunity to the toxins of the plasmodia rather than to actual infection by the organisms Repeated infections in youth and early adult life result in a considerable degree of immunity, but even in such individuals exposure to unwonted hardship or privation will often destroy the immunity evidently by influencing the defensive mechanism of the body, and symptoms of malaria will develop The examination of the blood of native races living in malarial localities as well as of Europeans will generally result in the demonstration that a considerable proportion of such individuals have the plasmodia in the blood although symptoms of infection are absent, and a very large proportion of such individuals are "carriers" of malaria the blood containing gametocytes These latent malarial infections are of the very greatest importance in the transmission of malaria and are considered more fully later in this contribution

As regards the occurrence of immunity to malarial infections it may be stated that certain individuals are naturally immune others may acquire an immunity while still others acquire an immunity to the toxin of the plasmodia but still may become infected and harbor the plasmodia in their blood for long periods of time without the appearance of symptoms of the infection

Factors Influencing the Transmission of Malaria

An immunity acquired for one species of plasmodium is not effective against the other species although there may be a slight heterologous immunity in some instances Thus if an individual has acquired an immunity to infection with *Plasmodium vivax* he is still susceptible to infection with *Plasmodium malariae*, *Plasmodium falciparum* or *Plasmodium ovale* In addition it has been demonstrated repeatedly experimentally that an immunity to one strain of plasmodium is not effective against other strains of the same species Thus James and Shute

(1927) and others have shown that patients treated for paresis by the injection of blood containing malaria plasmodia acquire an immunity to the strain of the plasmodium inoculated but not to other strains of the same species of plasmodium It is thus evident that although an individual may become immune to a strain of *Plasmodium vivax* for instance in the United States, he would not be immune to strains of the same species of plasmodium from other countries and even in the same country strains derived from different localities might produce an infection

As regards the length of protection afforded by an acquired immunity Boyd Stratman Thomas and Kitchen (1936)[40] have demonstrated that an immunity acquired to a strain of *Plasmodium vivax* was effective in preventing a clinical attack for as long as three years although infection may have occurred

Sinton Hutton and Shute (1939)[41] in using *Plasmodium ovale* in the treatment of paretics found that a high degree of resistance to reinoculation quickly developed when the same strain was used and a considerable resistance to other strains

The mechanism of the production of immunity in malaria is concerned very largely with the activity of the reticuloendothelial system but there is also evidence available that immune bodies are produced during a malarial infection as shown by the presence of complement fixing bodies in the blood serum of infected individuals As long ago as 1909 the writer[3] stated that immunity in malaria is due to the phagocytosis of the plasmodia by macrophages endothelial cells and leucocytes by antiplasmodial substances in the blood serum and by antitoxic substances in the serum which neutralize the malaria toxins and all of the evidence that has accumulated since then substantiates this statement The Taliaferros and Coggeshall and Eaton have shown that complement fixing bodies and precipitins are present in the blood serum of individuals infected with the malaria plasmodia but Boyd and Kitchen (1943)[1] have shown also that the inoculation of blood of patients who are able to withstand the injection of very large numbers of malaria plasmodia because of previous infection failed to prevent infection or modify the course of an existent infection

There is probably no infectious disease in which there are so many factors influencing the transmission of infection as in malaria These factors have to do with the development of the plasmodia in man the development of the plasmodia in the transmitting mosquitoes and with the recipient of the plasmodia from the mosquito

Factors Concerning the Development of the Plasmodia in Man —The most important factor influencing the transmission of the malarial infections so far as man is concerned is the occurrence in the blood of the plasmodia in the stage infective to the mosquito *i e* the gametocytes Unless these are present transmission is impossible as the mosquito cannot become infected Gametocytes

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Acquired immunity to malaria is frequently the result of repeated infections brought about by long residence in malarial localities. This type of immunity is most often illustrated in the natives of such localities and generally consists in a relative immunity to the toxins of the plasmodia rather than to actual infection by the organisms. Repeated infections in youth and early adult life result in a considerable degree of immunity, but even in such individuals exposure to unwonted hardship or privation will often destroy the immunity, evidently by influencing the defensive mechanism of the body and symptoms of malaria will develop. The examination of the blood of native races, living in malarial localities as well as of Europeans, will generally result in the demonstration that a considerable proportion of such individuals have the plasmodia in the blood although symptoms of infection are absent and a very large proportion of such individuals are "carriers" of malaria the blood containing gametocytes. These latent malarial infections are of the very greatest importance in the transmission of malaria and are considered more fully later in this contribution.

As regards the occurrence of immunity to malarial infections it may be stated that certain individuals are naturally immune, others may acquire an immunity while still others acquire an immunity to the toxin of the plasmodia but still may become infected and harbor the plasmodia in their blood for long periods of time without the appearance of symptoms of the infection.

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An immunity acquired for one species of plasmodium is not effective against the other species although there may be a slight heterologous immunity in some instances. Thus if an individual has acquired an immunity to infection with *Plasmodium vivax* he is still susceptible to infection with *Plasmodium malariae*, *Plasmodium falciparum* or *Plasmodium ovale*. In addition, it has been demonstrated repeatedly experimentally that an immunity to one strain of plasmodium is not effective against other strains of the same species. Thus James and Shute

species of plasmodium Thus it has been found that the optimum temperature for the development of *Plasmodium vivax in the mosquito is 25 C (77° F) and* if the external temperature is maintained at this height complete development will occur in about eleven days for *Plasmodium malariae* the optimum temperature is 22 C (72 F) and development is completed in from eighteen to twenty one days while for *Plasmodium falciparum* the optimum external temperature is 30 C (86 F) and complete development occurs in from ten to eleven days Temperatures between 10° C (48 F) and 18 C (64 F) markedly retard and in some instances prevent the development of the plasmodia in the mosquito but temperatures as low as 0 C (32 F) will not kill the plasmodia as removal of the infected mosquito to a favorable temperature results in the further development of the organisms Wenyon[19] has shown conclusively that infected mosquitoes kept at temperatures corresponding to winter temperatures for different periods of time and then kept at temperatures favoring the development of the plasmodia, become infective and that the plasmodia in the mosquitoes kept at the low temperature simply remained dormant and could remain in this condition for weeks and even months It is thus possible for the malaria plasmodia to remain alive in the mosquito through a winter and renew their development in the insect in the spring

While there is no evidence that the malarial infection in the mosquito is hereditary it is true that the plasmodia may remain alive in the infected mosquito for long periods of time Thus Mayne[0] found living sporozoites in mosquitoes kept in captivity for as long as ninety two days and it is probable that most infected mosquitoes remain so for as long as they live

The *numerical prevalence* of the species of mosquitoes which are most efficient hosts for the plasmodia has much to do with the transmission of the infection to man but it should be remembered that a few infected mosquitoes may transmit the plasmodia to many individuals for one infected insect may bite many human hosts and infect them That this must be so is proved by the fact that even in very malarial regions usually only a small proportion of the transmitting mosquitoes are found naturally infected

The *percentage of infected mosquitoes* has much to do with the transmission of the infection but considering the number of human carriers of the plasmodia in most endemic malarial regions and the chance of infection to mosquitoes the percentage of insects showing infection is remarkably low varying as a rule between 1 5 to 3 per cent However in some regions the percentage of infected mosquitoes is much higher at certain times and the writer has observed instances in which from 15 to 35 per cent of mosquitoes caught in hospitals in the tropics have been found infected The reason for the usual low percentage of infected mosquitoes in malarial regions is that only a small percentage become infective even after biting a malarial individual and because those that do be

usually begin to appear in the peripheral blood from three to ten days after the development of symptoms and after this time the infected individual is known as a carrier of malaria In the writer's experience gametocytes have been observed in the peripheral blood in a little over 33 per cent of all infections with the estivo autumnal plasmodia and in about 50 per cent of infections with the benign tertian plasmodium It is probably safe to state that from 35 to 50 per cent of malarial infections in man result in the formation of gametocytes and thus of carriers of the infection

Not only must gametocytes be present in the peripheral blood, in order that malaria be transmitted but there must be enough of them to infect mosquitoes It has been shown by Darling[17], Thomson[18] and others that there must be approximately one gametocyte to every 500 leucocytes, in order that the blood be infective to mosquitoes, and while more recent observations with the treatment of paresis by injection of the malaria plasmodia tend to show that mosquitoes may at times become infected when the peripheral blood contains a smaller number of gametocytes it is probably true that, in most instances at least one gametocyte to every 500 leucocytes must be present in the peripheral blood before mosquitoes can be infected

Another factor influencing the infection of the mosquito is the *sex* of the gametocytes There must be both male and female gametocytes present, and there must be a proper proportion of the two sexes Usually female gametocytes are most numerous and when not too numerous this condition is most favorable for infection of the mosquito The writer has observed that the usual proportion of females to males is from three to one to four to one but the proportion varies with the different species of plasmodia which may partially account for the relative rarity of certain species as *Plasmodium malariae*

The *age* of the gametocytes also influences the infection of the mosquito, as it has been found that the gametocytes are not generally infective to the transmitting insects when they first appear in the peripheral blood but that they must be about twelve days old as judged by the time of their appearance in the peripheral blood before they can undergo normal development in the mosquito

Factors Concerning the Development of the Plasmodia in the Mosquito —Very numerous are the factors that have to do with the development of the malaria plasmodia in the mosquito and it is probable that we are still ignorant of many factors that profoundly influence the transmission of malaria through their action upon the plasmodia after they reach the stomach of the transmitting insect

Temperature is a most important factor for it has been repeatedly demonstrated that unless the temperature is favorable the gametocytes will not develop normally in the mosquito and the insect will not become infective to man The temperature most favorable to development varies somewhat for each

governed by factors controlling resistance Of these the most important are long residence in a malarial locality which gives rise to an immunity to malarial infection in some individuals and factors having to do with a depression of the natural resistance of the individual The effect of long residence in malarial regions has already been considered and it has also been stated that even in individuals naturally resistant to malaria the resistance may be overcome by placing the individual under conditions leading to a depression of this resistance and the most important of these factors are exposure insufficient food over fatigue and mental anxiety and strain All of these conditions markedly lower resistance and render the recipient more susceptible to malarial infection

Pathology

The pathological changes occurring in the blood and viscera in malaria are very characteristic and this is especially true of the blood spleen and bone marrow The malaria toxin or toxins produce marked changes in the blood and blood forming organs and the growth of the plasmodia within the red blood corpuscles and the consequent destruction of the latter are responsible for the anemia which is always present in malarial infection

The Blood

As the parasites causing malaria develop within the red blood corpuscles causing their ultimate destruction a marked reduction in the number of these cells is invariably present in every acute infection Kelsch[22] was the first to demonstrate that the red cells are reduced after every febrile paroxysm due to malaria and if several paroxysms have occurred the total reduction may be very great Thus the writer has observed several instances in which the total number of erythrocytes averaged less than 1 000 000 per cu mm in pernicious malarial infections and in most cases in which the infection has lasted for a week or two the red cell count will average little over 2 000 000 per cu mm In pernicious infections the destruction of the red corpuscles may be very marked the count falling to a million or less within from thirty six to forty-eight hours after the initial paroxysm but such cases are rare In chronic infections there is always a more or less marked anemia and in acute infections that have remained untreated for several weeks the reduction in red blood corpuscles reaches a certain level and tends to remain at that level for an indefinite time provided pernicious symptoms do not develop After the infection is cured the red blood count in uncomplicated cases quickly regains normal

Along with the reduction in the number of red blood corpuscles there is a reduction in the number of leucocytes with a relative increase in the large mononuclear cells This increase has been regarded by some authorities as characteristic

come infective require more than one feeding upon the blood of the infected individual before infection occurs

The *particular species of Anopheles* present in any locality has a marked influence upon the transmission of malaria It has been proved by numerous observers that certain species of *Anopheles* are much better transmitters of the plasmodia than are others and that certain species may transmit certain species of the plasmodia with ease, while another species of plasmodia can only be transmitted with difficulty if at all Thus in India *Anopheles culicifacies* is found naturally infected with malaria plasmodia in as high as six per cent of the insects examined in malarial localities while *Anopheles rossi*, in the same localities is seldom found naturally infected with these parasites In the United States the most common transmitter of malaria is *Anopheles quadrimaculatus* while *Anopheles crucians* is seldom found naturally infected and is a very poor transmitter of the plasmodia *Anopheles quadrimaculatus* can transmit *Plasmodium vivax Plasmodium malariae* and *Plasmodium falciparum* with equal facility while *Anopheles punctipennis* has been found an efficient host of *Plasmodium vivax* and *Plasmodium falciparum* but not of *Plasmodium malariae*

Humidity affects the development of the malaria plasmodia in the mosquito and thus influences the transmission of the infection It acts by influencing the reproduction and biological activities of the mosquito and also by so affecting the internal temperature of the mosquito as to influence the development of the gametocytes as suggested by Christophers [1]

The *habits of the anopheline mosquitoes* transmitting malaria influence the number of infections in different localities Mosquitoes that live near the habitations of man are better transmitters of malaria than those living at a distance from human habitations Thus *Anopheles maculipennis* and *Anopheles quadrimaculatus* the most common transmitters of malaria in Europe and the United States respectively are domestic species living close to and frequenting the habitations of man while species like *Anopheles bifurcatus* and *Anopheles umbrosus* are much less concerned in the transmission of malaria because these species generally live in the open or in forests and are not so apt to come into contact with man as the domestic species

The factors mentioned are not all that have to do with the development of the malaria plasmodia in the mosquito but are probably the most important and well illustrate the complexity of the subject of the transmission of the infections

Factors Concerning the Recipient of the Plasmodia — That there are many factors governing the development of the plasmodia in the recipient of the infection is undoubted and many such factors probably are unknown at present However we do know that the successful implantation of malaria in man depends upon the susceptibility of the recipient to the infection and that this is

increased in amount albumin appears and hyaline and granular casts are observed Albumin and casts also occur in severe tertian and quartan infections and are almost invariably present in pernicious estivo-autumnal malaria

Morbid Anatomy

The pathological changes observed in the various organs of the body after death from malaria are most characteristic and a diagnosis of such infections is easily possible from the changes observed at autopsy provided the infection has lasted for several days In very acute fatal cases the macroscopic changes are not characteristic and the diagnosis rests upon the results of microscopic examinations of the blood and viscera

The *brain* shows marked congestion of the capillaries and small hemorrhages are present in the parenchyma due to the blocking of the capillaries with parasite laden erythrocytes leucocytes and free pigment In many cases the pigmentation is so marked as to give the cortex of the brain a grayish or brownish appearance Microscopically the capillaries are observed to be filled with red blood cells containing plasmodia phagocytic cells and blocks of pigment and thrombi caused by the accumulation of these elements are frequently noted

The *lungs* do not show any characteristic lesions beyond the presence of areas of congestion and microscopically the presence of infected red blood corpuscles pigmented leucocytes and free pigment within the capillaries In some instances in which a pneumonia has complicated a malarial infection the exudation in the alveoli differs from that usually noted in the presence of the elements noted above but there is little reason for believing that the malaria plasmodia per se ever produce a typical lobar pneumonia as has been claimed by some observers

The *liver* generally is enlarged pigmented and congested In long continued infections the pigmentation is very marked the organ being dark green or almost black in color Microscopically the capillaries contain many macrophages filled with plasmodia and pigment infected erythrocytes and free pigment The liver cells show cloudy swelling or fatty degeneration with areas of necrosis apparently due to the malaria toxin Besides the malarial pigment present there is much yellowish brown pigment due to the degeneration of red blood corpuscles but this pigment is not characteristic of malaria

The *spleen* probably shows the most marked and characteristic changes observed in any of the viscera It is generally enlarged sometimes enormously so and in long continued infections is dark blue or almost jet black in color due to pigmentation In many chronic infections the cut surface of this organ is the color of tar due to the intense pigmentation but in acute pernicious infections the pigmentation may be scarcely noticeable macroscopically In acute infec

of malarial infection, but it occurs in many other parasitic infections having no connection with malaria. During the febrile paroxysm there is often a marked leucocytosis.

The hemoglobin, especially in the severe forms of estivo-autumnal infection, is reduced in amount from ten to forty per cent within a few days, but in some severe and even in fatal cases, where the infection has only lasted for a few days, there may be but little reduction in the hemoglobin. In long continued infections the hemoglobin usually is reduced proportionately with the red blood corpuscles.

The morphological changes in the uninfected red corpuscles consist in more or less poikilocytosis and an anemic appearance of the center of the red cell. The normal hyaline appearance of this portion of the erythrocyte is greatly accentuated, and the tyro in microscopic work is apt to mistake this appearance for hyaline stages of the malaria plasmodia. In severe cases of malaria nucleated red corpuscles may be observed, and the blood picture may resemble that of primary pernicious anemia. As already stated, in tertian infections the infected cell is enlarged and presents eosinophilic staining granules known as Schuffner's dots, while in the estivo-autumnal infections the infected red cell, while not enlarged, may present a basophilic stippling, sometimes known as Maurer's dots.

A characteristic morphological feature of malarial infections is the occurrence in the peripheral blood and in the capillaries of the viscera of leucocytes containing much pigment and even malaria plasmodia which have been phagocyted. This pigment is derived from the hemoglobin of infected red corpuscles through the action of the plasmodia and is liberated in the blood plasma at the time of segmentation. Most of the pigment is taken up by the polymorphonuclear leukocytes, but in all infections some of the pigment remains free in the blood and in pernicious cases often blocks the small capillaries of the brain. Large phagocytic cells, known as macrophages, are present in the capillaries of the spleen and other viscera, and these often contain entire plasmodia as well as enormous amounts of pigment. The pigment present in malaria is known as melanin and occurs in the form of granules, grains, minute rods and irregular clumps. It varies in color from yellowish brown to almost black.

The Urine

In most cases of tertian and quartan malaria no important pathological changes occur in the urine. Polyuria may be present during the decline in the temperature and the chlorides are increased in most instances. On the other hand, in most estivo-autumnal infections and especially in those presenting pernicious symptoms pathological changes in the urine are frequently encountered. During the paroxysm the specific gravity is increased, urea is

laria are found upon autopsy to show evidences of such infection In these cases in which the infection is latent in character the writer has shown that the spleen and liver may show pathological lesions which are characteristic of malaria The *spleen* may be slightly enlarged and show a little pigmentation while microscopical examination demonstrates the presence of intense congestion of the sinuses together with pigmentation The capillaries and sinuses contain parasite infected erythrocytes and pigmented leucocytes but in much smaller number than in acute infections In the *liver* the capillaries show a few *pigmented leucocytes and some free pigment but no infected erythrocytes* are observed In the sections of the spleen the entire human life cycle of the plasmodia can be traced and as in some of the cases examined no symptoms had been noted for weeks these observations demonstrate that both *Plasmodium vivax* and *Plasmodium falciparum* may undergo their entire human life cycle in the spleen without the production of symptoms for considerable periods of time a fact of much importance in the explanation of relapses in malarial infections

Occurrence of Plasmodia in Lower Animals (Reservoirs of Infection)

It has been stated by several observers that they have studied malarial infections in man that apparently were acquired in uninhabited regions and this has lead to the belief by some authorities that in such regions birds or monkeys may be infected with the malaria plasmodia of man and may act as reservoirs of infection or serve to perpetuate the parasites causing human malaria in such regions It is well known that birds and monkeys are infected with plasmodia that closely resemble in morphology the malaria plasmodia of man but all attempts to transfer any of the human species to animals have failed with the exception of the doubtful experiment of Mesnil and Roubaud (1920)[43] who claimed to have infected a chimpanzee with *Plasmodium vivax* and the apparent success of Taliaferro and Taliaferro (1934)[44] in transmitting *Plasmodium falciparum* to a species of monkey in Panama More recently Rodhain and Muylle (1939)[45] claim to have infected a chimpanzee with *Plasmodium vivax*

That it is possible to infect man with species of plasmodia occurring in lower animals is proven by the experiments of Knowles and Das Gupta (1932)[46] Van Royen and Pile (1935) Chopra (1937) Milam and Coggeshall (1938) Rodhain (1940) and others who have transferred *Plasmodium knowlesi* of the monkey to man and produced in the latter typical symptoms of such infection This plasmodium has been employed in the treatment of paretics by most of these investigators and it is probable that this species was concerned in those cases of malaria contracted in regions uninhabited by man already mentioned

tions the organ is greatly congested, but in long continued infections the congestion may not be marked Microscopically the capillaries of the organ are filled with infected erythrocytes, macrophages, pigmented leucocytes and free pigment while areas of hemorrhage are frequently observed Large macrophages containing infected red blood corpuscles and enormous amounts of pigment are a characteristic feature of the pathology of the spleen This organ, like the liver shows the presence of large amounts of the golden brown or yellowish pigment derived from the degeneration of uninfected red blood corpuscles

The *stomach* and *intestines* may show marked lesions due to malarial infection in those instances in which marked intestinal disturbances were present before death The mucous membrane especially of the intestine may be greatly congested and more or less pigmented while there may be areas of ulceration and necrosis present Microscopically the capillaries of the mucous membrane of the stomach and intestine may be greatly congested by infected erythrocytes pigmented leucocytes and free pigment, and areas of necrosis may be observed caused by the blocking of the capillaries with these elements In the writer s experience changes in the stomach and intestine which are visible macroscopically are very rare in pernicious malarial infections

The *kidneys* in pernicious cases of malaria present marked lesions, consisting essentially of the usual lesions noted in an acute or subacute parenchymatous nephritis associated with those which are peculiar to the malarial infection, as pigmentation of the epithelial cells lining the tubules intense engorgement of the capillaries especially of those in the Malpighian tufts with infected erythrocytes pigmented leucocytes and free pigment

The *bone marrow* in long continued malarial infections shows marked changes The color varies from a dark red to almost black, due to pigmentation, while the capillaries and marrow pulp contain infected erythrocytes macrophages, free pigment and nucleated red blood corpuscles

The Pathology of Chronic Malarial Infections

The pathology of *chronic malarial infections* is characterized by marked anemia enlargement of the spleen and liver with marked pigmentation of these organs while the kidneys become hypertrophied and the cortex of the brain pigmented The enlargement of the spleen may be excessive, the writer having observed instances in which the spleen weighed ten pounds or more In very old infections cirrhotic changes occur in the liver spleen and kidneys

The Pathology of Latent Malarial Infections

In regions in which malaria is endemic it sometimes happens that patients dying from other diseases who during life have presented no symptoms of ma

laria, are found upon autopsy to show evidences of such infection In these cases in which the infection is latent in character the writer has shown that the spleen and liver may show pathological lesions which are characteristic of malaria The *spleen* may be slightly enlarged and show a little pigmentation while microscopical examination demonstrates the presence of intense congestion of the sinuses together with pigmentation The capillaries and sinuses contain parasite infected erythrocytes and pigmented leucocytes but in much smaller number than in acute infections In the *liver* the capillaries show a few pigmented leucocytes and some free pigment but no infected erythrocytes are observed In the sections of the spleen the entire human life cycle of the plasmodia can be traced and as in some of the cases examined no symptoms had been noted for weeks these observations demonstrate that both *Plasmodium vivax* and *Plasmodium falciparum* may undergo their entire human life cycle in the spleen without the production of symptoms for considerable periods of time a fact of much importance in the explanation of relapses in malarial infections

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tions the organ is greatly congested, but in long continued infections the congestion may not be marked. Microscopically the capillaries of the organ are filled with infected erythrocytes, macrophages, pigmented leucocytes and free pigment, while areas of hemorrhage are frequently observed. Large macrophages containing infected red blood corpuscles and enormous amounts of pigment are a characteristic feature of the pathology of the spleen. This organ like the liver shows the presence of large amounts of the golden brown or yellowish pigment derived from the degeneration of uninfected red blood corpuscles.

The *stomach* and *intestines* may show marked lesions due to malarial infection in those instances in which marked intestinal disturbances were present before death. The mucous membrane, especially of the intestine, may be greatly congested and more or less pigmented, while there may be areas of ulceration and necrosis present. Microscopically the capillaries of the mucous membrane of the stomach and intestine may be greatly congested by infected erythrocytes, pigmented leucocytes and free pigment, and areas of necrosis may be observed caused by the blocking of the capillaries with these elements. In the writer's experience changes in the stomach and intestine which are visible macroscopically are very rare in pernicious malarial infections.

The *kidneys* in pernicious cases of malaria present marked lesions, consisting essentially of the usual lesions noted in an acute or subacute parenchymatous nephritis, associated with those which are peculiar to the malarial infection, as pigmentation of the epithelial cells lining the tubules, intense engorgement of the capillaries, especially of those in the Malpighian tufts, with infected erythrocytes, pigmented leucocytes and free pigment.

The *bone marrow* in long continued malarial infections shows marked changes. The color varies from a dark red to almost black, due to pigmentation, while the capillaries and marrow pulp contain infected erythrocytes, macrophages, free pigment and nucleated red blood corpuscles.

The Pathology of Chronic Malarial Infections

The pathology of *chronic malarial infections* is characterized by marked anemia, enlargement of the spleen and liver, with marked pigmentation of these organs, while the kidneys become hypertrophied and the cortex of the brain pigmented. The enlargement of the spleen may be excessive, the writer having observed instances in which the spleen weighed ten pounds or more. In very old infections cirrhotic changes occur in the liver, spleen and kidneys.

The Pathology of Latent Malarial Infections

In regions in which malaria is endemic it sometimes happens that patients dying from other diseases, who during life have presented no symptoms of ma-

been shown conclusively that a period of between eighteen and twenty-one days usually elapses after exposure, before the men begin to appear in any number upon sick report with malaria and that the greatest number of infections come on sick report within one month after exposure While this is true it should not be forgotten that the incubation period may be greatly prolonged and undoubted cases have been observed where clinical symptoms of malaria did not appear until many weeks or even months have elapsed since exposure to infected mosquitoes

Symptoms of Vivax or Tertian Malaria

This form of malaria is due to the tertian plasmodium or *Plasmodium vivax* and the paroxysms of fever occur at the time of segmentation of this parasite

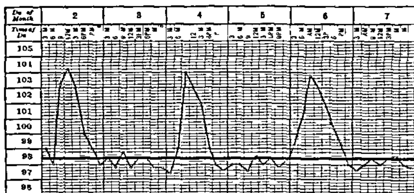


Fig 22 — Vivax or Tertian Malarial Fever

which occurs at the end of every forty-eight hours (see chart Fig 2) Tertian malarial infections are the mildest of all malarial infections but some cases have been recorded of fatal results from infection with this species of plasmodium While the danger to life in the vast majority of cases is negligible the symptoms that may be present during a paroxysm are often severe and may cause great anxiety to the patient and attending physician unless the nature of the disease has been determined by a microscopical examination of the blood When there is an infection with two generations of this plasmodium which segment on successive days the tertian type of paroxysm is lost and a paroxysm occurs every day causing a quotidian fever

Incubation Period — The incubation period of infections with the tertian plasmodium varies considerably When the infection is produced by the direct subcutaneous inoculation of blood containing the parasite the incubation period has been found to vary between eleven and twenty-one days the average period

While at the present time there is no proof that any of the species of malaria plasmodia occurring in monkeys are identical with those infecting man the fact that monkey malaria is transmitted by anopheline mosquitoes should be remembered in conducting surveys for the determination of malaria infected mosquitoes in regions where monkeys are prevalent, for such mosquitoes might be infected with the plasmodia of monkeys rather than those infecting man

CLINICAL SYMPTOMS OF MALARIAL INFECTION

Clinically malarial infections may be divided into intermittent, remittent, sub continued and continued fevers but such a classification gives no idea of the exact type of malaria present as any malarial fever may present any of the types of fever mentioned, according to the number of generations of plasmodia which may be present If several generations of plasmodia are present, the fever is usually sub continued or continued in character, while if only a single generation is present, the fever is always intermittent in type In estivo-autumnal tertian malaria, owing to the short intervals between the paroxysms even an infection with a single generation of plasmodia may give rise to a remittent type of fever and the term remittent malaria" is often applied to estivo autumnal infections However it is far better to classify the malarial fevers from an etiological standpoint and this method will be followed in this contribution Thus classified we have four generally accepted types of malarial fever each due to its own peculiar species of plasmodium and to which the terms vivax malariae falciparum and ovale malaria are applied

Incubation Period

The incubation period of the malarial fevers varies for each type and will be considered in discussing the symptomatology of vivax, malariae and falciparum malaria but it may be stated that for all types the incubation period varies greatly under natural conditions and its extreme limits are unknown for any type of the infection

What we know concerning this subject has been largely derived from the experimental production of malaria in man by the direct inoculation of blood containing the plasmodia and by the bites of experimentally infected mosquitoes and such observations may not be altogether reliable when relied upon to determine the natural period of incubation It is true however, that the periods of incubation thus determined agree quite well with those observed under natural conditions and we know that though the period may be greatly prolonged, it is usually between two and four weeks after exposure for all types of malaria In troops serving in tropical countries, where malaria is severely endemic, it has

the fever begins to decline perspiration begins to appear upon the forehead face and hands and the severity of the other symptoms decreases As the fever reaches the normal point, the perspiration becomes very profuse the entire body being covered with it and in some cases it is so marked as to be seen trickling in tiny rivulets from the arms and legs In some cases this stage is accompanied by symptoms of collapse the respirations becoming rapid and shal low the pulse thready and weak and the extremities cold but these alarming symptoms occur in only a very small number of cases With the decline of the fever and the appearance of profuse perspiration all disagreeable symptoms dis appear *and the patient rapidly recovers from the paroxysm so that between* paroxysms the patient feels fairly well During the first twenty four hours after the fever reaches normal polyuria frequently is noted

The entire tertian paroxysm lasts from ten to fourteen hours in the vast majority of cases but in severe infections it may last for twenty four hours The physical examination may show an enlarged spleen but if there have been only one or two paroxysms the spleen may not be appreciably enlarged Al buminuria occurs in a small proportion of tertian infections and hyaline and granular casts sometimes may be found during the height of the fever

It often happens that an individual becomes infected with two generations of tertian plasmodia segmenting at different times and when this occurs we may have a quotidian paroxysm in a tertian infection the two generations seg menting upon successive days Such double infections often cause much confu sion in diagnosis the quotidian temperature being thought to be due to other infections and the presence of malaria overlooked It has also been observed that tertian malaria produced by the subcutaneous injection of blood contain ing the plasmodia as in the treatment of paretics with malaria frequently gives rise to a quotidian type of temperature probably caused by delay in segmenta tion of some of the plasmodia injected and the same phenomenon has been noted in experimental infections brought about by the bites of mosquitoes in fected with this plasmodium

Even in typical single infections with the tertian plasmodium it should be remembered that the paroxysms do not occur at exactly forty eight hour inter vals but in approximately that time

Symptoms of Malariae or Quartan Malaria

This comparatively rare type of malaria is caused by the quartan plasmo dium or *Plasmodium malariae* and is characterized by paroxysms of chill fever and sweating occurring at the time of segmentation of the plasmodia or ap proximately every seventy two hours However it should be remembered that infection with two generations of this parasite segmenting upon successive days will cause paroxysms upon two successive days followed by a day of normal tem

being about eleven to twelve days In some infections, produced in treating paretics with *Plasmodium vivax* by direct inoculation of the blood from infected individuals, the incubation period has been as short as six days and as long as twenty one days

When the infection is produced by the bite of infected mosquitoes symptoms begin to appear in from nine to twenty four days the average period of incubation being from fourteen to seventeen days In nature it has been observed that tertian infections usually present symptoms in from two to three weeks after exposure and this period may be taken as the usual incubation period under natural conditions

Symptoms It is in this type of malaria that the typical malarial paroxysm consisting of the three classical stages of chill, fever and sweating is best illustrated Prodromal symptoms, consisting of loss of appetite general malaise and dull headache may have been noted for a few days before the onset of the paroxysm The latter generally begins suddenly with a severe shaking chill the patient complaining of the cold, even though the thermometer shows that his temperature is steadily rising The face is cyanotic, the lips blue, the hands and feet feel cold and appear cyanotic, while the well known condition called "goose flesh" is marked over the skin of the trunk and extremities The pulse is rapid of low tension and may be irregular The temperature rises steadily during the cold stage but does not reach its maximum until the chill has disappeared The urine is increased in amount and of lower specific gravity than is normal The duration of the chill, or cold stage varies from one quarter of an hour to two hours, the average period being about half an hour

The hot stage is first noticed by the patient as flushings of heat succeeded by cold sensations but soon the sensation of heat is continuous and the temperature reaches 104° or 105° F in the average infection The face becomes flushed and congested, the skin of the entire body reddened and hot and dry to the touch The eyes are brilliant in most instances and the conjunctivae markedly congested The respirations are increased in number, while the pulse is increased in frequency, of increased tension and often dicrotic Headache is generally intense and epistaxis may occur The congestion of the lungs often causes a slight cough which may lead to the suspicion that the attack is one of pneumonia In severe cases delirium may be present or a semi comatose condition may develop but in tertian malaria such symptoms are rare Skin eruptions may occur, most frequently erythematous or urticarial in character while herpes is a very common condition, generally occurring on the lips but often on other parts of the body The duration of this stage varies but it generally lasts for from four to six hours

The sweating stage commences as the temperature begins to decline, but instances have been observed in which the fever reached its height during this stage This stage of the paroxysm generally lasts from two to three hours As

the fever begins to decline perspiration begins to appear upon the forehead face and hand and the severity of the other symptoms decreases As the fever reaches the normal point the perspiration becomes very profuse the entire body being covered with it and in some cases it is so marked as to be seen trickling in tiny rivulets from the arms and legs In some cases this stage is accompanied by symptoms of collapse the respirations becoming rapid and shallow the pulse thready and weak and the extremities cold but these alarming symptoms occur in only a very small number of cases With the decline of the fever and the appearance of profuse perspiration all disagreeable symptoms disappear, and the patient rapidly recovers from the paroxysm so that between paroxysms the patient feels fairly well During the first twenty four hours after the fever reaches normal polyuria frequently is noted

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It often happens that an individual becomes infected with two generations of tertian plasmodia segmenting at different times and when this occurs we may have a quotidian paroxysm in a tertian infection the two generations segmenting upon successive days Such double infections often cause much confusion in diagnosis the quotidian temperature being thought to be due to other infection and the presence of malaria overlooked It has also been observed that tertian malaria produced by the subcutaneous injection of blood containing the plasmodia as in the treatment of paretics with malaria frequently gives rise to a quotidian type of temperature probably caused by delay in segmentation of some of the plasmodia injected and the same phenomenon has been noted in experimental infections brought about by the bites of mosquitoes infected with this plasmodium

Even in typical single infections with the tertian plasmodium it should be remembered that the paroxysms do not occur at exactly forty-eight hour intervals but in approximately that time

Symptoms of Malariae or Quartan Malaria

This comparatively rare type of malaria is caused by the quartan plasmodium or *Plasmodium malariae* and is characterized by paroxysms of chill fever and sweating occurring at the time of segmentation of the plasmodia or approximately every seventy two hours However it should be remembered that infection with two generations of this parasite segmenting upon successive days will cause paroxysms upon two successive days followed by a day of normal tem

perature while if more than two generations of the plasmodia are present, a quotidian or irregular fever may result In the writer s experience the vast majority of quartan infections are infections with a single generation of the plasmodium

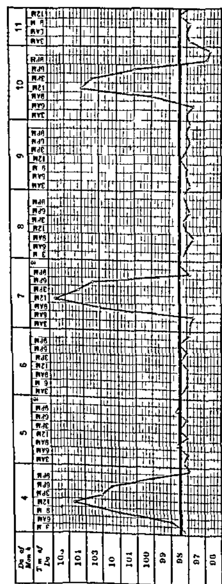


Fig 23 — Quartan Malariae or Malarial Fever

Incubation Period — The incubation period of quartan malaria after the subcutaneous inoculation of blood containing the plasmodia has been found to vary between ten and eighteen days the average period being fourteen days After experimental infection brought about through the bites of infected mosquitoes, the incubation period has been found to be about twenty-one days

Symptoms — The symptoms of quartan malaria are very similar to those occurring in the tertian type there being the same sequence of chill, fever and sweating in uncomplicated infections, but the symptoms are apt to be more severe, especially affecting the nervous system and intense headache and mild delirium during the height of the fever are observed much more frequently in this type of malaria Aside from these differences the symptoms are practically the same in quartan as in tertian malaria and repetition is needless The quartan paroxysm usually lasts from eight to ten hours, but in heavy infections the entire paroxysm may cover nearly twenty four hours Fatal cases of quartan malaria occur relatively more frequently than fatal cases of tertian malaria but are very rare as compared with infections due to the estivo-autumnal plasmodia

Symptoms of the Sub-Tertian Form of Falciparum or Estivo-Autumnal Malaria

As the writer has stated he believes that estivo-autumnal fevers are caused by two different plasmodia one completing its human life cycle in twenty four

hours and causing in typical cases a quotidian fever and one completing its human life cycle in approximately forty-eight hours and causing a tertian fever The quotidian plasmodium *Plasmodium falciparum quotidianum* is of very rare occurrence in comparison with the tertian species *Plasmodium falciparum* in the writer s experience over ninety five per cent of all estivo-autumnal infec tions being due to the latter species It is *Plasmodium falciparum* also that causes the greatest number of pernicious malarial infections although it is prob able that relatively the quotidian sub species causes a greater number of deaths as this parasite multiplies more rapidly and is more resistant to treatment

Period of Incubation —After the subcutaneous inoculation of blood con taining *Plasmodium falciparum* it has been found that the period of incubation before the appearance of symptoms has varied from three to ten days the aver age period being about five days In infections produced through the bites of infected mosquitoes the period of incubation has varied between seven and fifteen days the average period being from ten to twelve days In infection with this species the period may be greatly prolonged and the writer has observed a case in which the period of incubation must have covered at least seven months In the case of troops operating in regions heavily infested with this form of malaria it has been repeatedly noted that the men began to come on sick report in from ten to twelve days after exposure so that it is probable that the incuba tion period under natural conditions is like that produced by the bite of the mosquito experimentally Shorter periods of incubation have been noted after natural infection eight to nine days having been recorded by several observers

Symptoms —The sub tertian type of malaria is the predominating form of malarial infection in nearly all tropical localities and in most sub-tropical re gions In the tropics this form of infection occurs throughout the year but in sub tropical and temperate regions it occurs mostly during the months of July August September and October hence the name summer autumn fevers In the older writings upon this type of malaria the fever was distinguished clini cally under the term remittent malarial fever while tertian and quartan malaria were known as intermittent malarial fevers The term remittent malaria should be abandoned as applied to estivo-autumnal infections as the fevers caused by the estivo-autumnal parasites are as truly intermittent when uncomplicated as are tertian and quartan fevers It is true however that owing to infection with more than one generation of the plasmodia and the tendency to irregular segmentation in *Plasmodium falciparum* the temperature curve in this form of malarial fever is more apt to become irregular or remittent than in tertian or quartan infections

The prodromal symptoms of this form of estivo-autumnal malaria are similar to those of tertian and quartan malaria but often in this form of malaria such symptoms are absent and the patient is suddenly prostrated In most infections

stages of chill fever and sweating can be differentiated but they often merge into one another to such an extent as to be practically indistinguishable

The cold stage commences with yawning and a feeling of general malaise accompanied by nausea and in some instances by vomiting The severe shaking chill so characteristic of tertian and quartan infections, is often absent there being chilly sensations located along the spine and a sensation of cold especially noted in the trunk and legs Headache is intense, and mental depression is often present The pulse is increased in frequency and decreased in tension while the respirations are increased in number The face appears cyanotic, the eyes brilliant and the skin of the body and extremities shows the condition known as goose flesh The temperature gradually rises during this stage to 103° F or over The average duration of the cold stage is about half an hour

The hot stage commences with localized flushings of heat which soon become general The face is flushed the eyes brilliant and the skin of the entire body is flushed hot and dry Marked mental symptoms may be present, consisting of delirium or somnolence and headache is generally intense and sometimes almost unbearable There is severe neuralgic pain in the back and limbs and the temperature during this stage generally reaches 104° F or higher Severe vomiting may occur and diarrhea is sometimes noted The pulse is increased in rapidity and dicrotic in character, while the respirations are rapid and there may be marked dyspnea The urine contains albumin in many infections and hyaline and granular casts may be present The hot stage lasts for from sixteen to twenty four hours or even longer

The sweating stage is not as well marked in this form of malaria as in tertian and quartan infections but the symptoms are similar The temperature declines rapidly accompanied by slight perspiration in most instances while the disagreeable symptoms of the infection disappear and the patient feels about as well as usual However this period of absence of symptoms is very short extending over only a few hours when the paroxysm is repeated The paroxysms of sub tertian malaria generally occur toward evening extend throughout the next day and terminate during the early morning hours of the third day, covering in all thirty six hours or more and recurring every forty-eight hours

The temperature curve in the sub tertian form of estivo-autumnal malaria is characteristic and is one not encountered in any other febrile condition The writer, who has observed thousands of cases of this type of malaria, considers that the temperature curve in uncomplicated infections is absolutely diagnostic, and that it is possible to differentiate this infection from others by the temperature chart alone (see chart Fig 24) The fever rises rapidly during the first two hours of the paroxysm to 103° F or higher after which there is a period of two or more hours during which slight oscillations occur in the curve At the end of this time the fever falls suddenly a degree or more, and this fall may be

mistaken for the crisis However this fall or pseudocrisis is followed by another rise in temperature to a point as high or higher than the preceding highest point after which the true crisis occurs and the temperature falls rapidly to normal or below normal Thus it will be seen that the temperature curve may be divided into five stages the initial rise the stage of oscillation the pseudocrisis the pre-critical rise and the true crisis

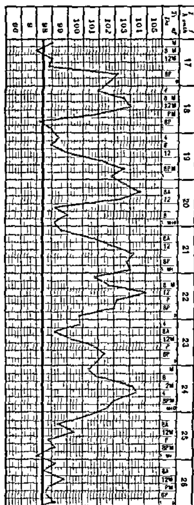


Fig 24 — Falciparum or Tertian Estivo-Autumnal Malarial Fever

Unfortunately many cases of subtertian malaria occur in which more than one generation of the plasmodia are present and the temperature then loses its characteristic curve Marked deviations from the classical temperature curve are also caused by insufficient treatment with *quinine* and by the anticipation or retardation of the segmentation of the plasmodia as well as by the natural resistance of the patient to the malaria toxin In order to be of any value in diagnosis the temperature in this type of malaria should be taken every three hours while active symptoms are present as otherwise the peculiar curve will not be demonstrated

Symptoms of the Quotidian Form of Falciparum or Estivo-Autumnal Malaria

This type of malarial infection is caused by a sub species of *Plasmodium falciparum* called *Plasmodium falciparum quotidianum* and is characterized by paroxysms occurring every twenty four hours due to the segmentation of the parasites The symptoms are similar *to those occurring in sub-tertian estivo-*autumnal malaria but the chill is usually more severe and sweating more pronounced The temperature rises rapidly to 103 F or more and falls within a few hours to normal or below the entire paroxysm not lasting more than twelve hours in most instances (see chart Fig 25) In very severe or pernicious forms

of this type of malaria the attacks tend to merge and the temperature to become more or less remittent or continuous Quotidian estivo-autumnal malaria, while not as frequently pernicious in type as the sub tertian form, is more fatal, when it does assume pernicious characteristics, owing to the rapid multiplication of the plasmodia and the fact that it is more resistant to treatment

Symptoms of Plasmodium Ovale Malaria

The symptoms of malaria produced by infection with *Plasmodium ovale* resemble those of tertian malaria The paroxysms occur approximately every forty eight hours and there is a well defined chill, followed by fever and sweating Although all of the symptoms which are noted in malaria caused by *P vivax* are observed in infections with this plasmodium, *P ovale* the paroxysms usually are not as severe and are of shorter duration than those caused by *P vivax* However, so far as the clinical symptoms, which are observed, are concerned it would be impossible to differentiate this form of malaria from benign tertian malaria The diagnosis must be made on the basis of the morphological appearance of the parasites as seen under the microscope

Symptoms of Pernicious Malaria

This term is applied to those malarial infections in which the symptoms are so severe as to endanger life or actually cause the death of the patient Any of the species of malaria plasmodia may cause such symptoms but the great majority of pernicious infections are due to the estivo-autumnal plasmodia Either the sub tertian or quotidian plasmodium may cause pernicious symptoms, but the vast majority of such infections are due to the sub tertian plasmodium, *Plasmodium falciparum*, as this is the most common species causing estivo-autumnal malaria Any infection with the estivo-autumnal plasmodia should be considered a serious infection as at any time pernicious symptoms may develop which may cause the death of the patient within a few hours Pernicious symptoms are most apt to develop in patients with a history of repeated attacks of malaria but fatal symptoms may appear during the initial attack

The exact cause of development of pernicious symptoms is still a mooted question but several causes probably operate in most cases Undoubtedly the localization of the plasmodia in the capillaries of the brain with the consequent accumulation of pigment parasites and leucocytes and the blocking of these capillaries is responsible for the cerebral type of pernicious malaria but the amount and character of the toxin or toxins produced by the plasmodia the excessive number of parasites present the lack of resistance of the patient and local conditions favoring the growth of the plasmodia or decreasing the resist

ance of the patient are also undoubtedly operative in most instances It is a well known fact that falciparum infections are much more pernicious in some localities than in others and the exact reason for this fact is still a mystery There is some evidence in support of the view that in such localities the strain of plasmodia is a very virulent one but why it should be so is still unexplained

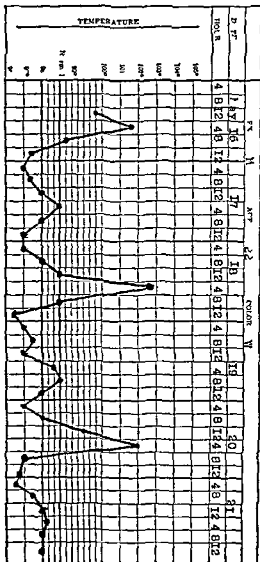


FIG 25(a) — Temperature chart of a patient infected with *Plasmodium ovale* Note general resemblance to the temperature chart of infections with *P vivax* (see Fig 22) but with lower range in the temperature and the shorter febrile period

The pernicious types of malaria are generally classified according to the most marked symptoms present Thus we have algid bilious cardialgic choleraic comatose delirious dysenteric eclamptic hemiplegic hemorrhagic and pneumonic pernicious malaria but it should be remembered that etiologically these forms are not disease entities but simply indicate the most prominent symptoms which may be present As the names attached to these various forms of pernicious malaria sufficiently indicate the character of the clinical symptoms present only the most important forms will be briefly described

The *algid* form of pernicious malaria is one frequently encountered in the southern part of the United States and in the tropics It is characterized by

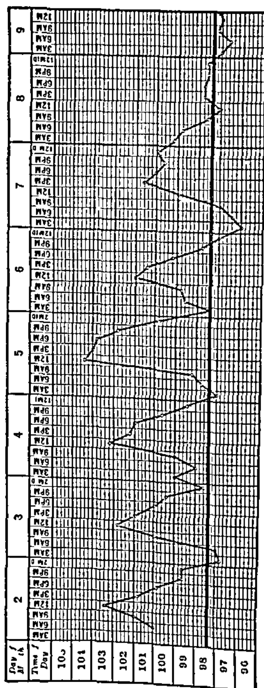


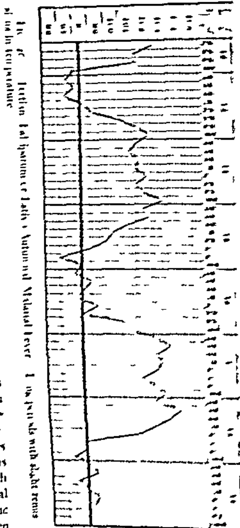
FIG 25 — Quotidian Falciparum Æstivo-Autumnal Malarial Fever

symptoms of profound collapse almost from the very onset of the paroxysm and is almost invariably fatal, unless treatment is administered very promptly The symptoms generally develop after one or more previous attacks of malaria, but they may be the first symptoms in a primary attack Clinically, the patient presents the classical symptoms of profound collapse noted in shock or following diseases like cholera or acute dysentery Profuse perspiration and mental apathy or stupor are prominent symptoms and death generally occurs in untreated cases within twenty four to thirty six hours but may occur within a very few hours after the appearance of the symptoms of collapse

The *comatose* form is the most common form of pernicious malaria and may occur as a sudden attack of coma or this condition may develop gradually during an ordinary paroxysm of malarial fever In those instances in which the condition develops suddenly the patient becomes suddenly unconscious while going about his usual occupation falls to the ground and in the fatal cases does not regain consciousness It is this form of malaria that has often been mistaken for apoplexy or an uremic attack in regions where it does not frequently occur The face is deeply congested the pupils contracted the pulse rapid and increased

in tension and the respirations irregular and … irregular and often little elevated above normal. … less treatment is administered promptly, death …

In the form of comatose pernicious malaria which develops gradually during an ordinary attack of the infection, the pernicious symptoms appear so gradually that sometimes the patient is in imminent danger before the condition is recognized. The nervous symptoms as headache and restlessness increase, and mental depression or a mild form of delirium are precursors of the fatal coma that is approaching. The patient becomes drowsy, is aroused with difficulty, and finally unconsciousness becomes complete, the body lying quietly, or there may be twitching of the muscles or aimless movements of the arms and legs. Hemiplegia or complete paralysis may be present. In some cases the face is congested and the pupils contracted or equally dilated, while in others the face is pale and the pupils equally contracted. The pulse is increased in tension at first but becomes rapid and of small volume as death approaches. The respirations are generally quiet and decreased in frequency, although in some instances they may be hurried and stertorous in character. In many cases in which there is a history of repeated malarial attacks the skin has a marked icteric hue and such cases have often been



Italian Estivo-Autumnal Malarial Fever. Long periods with slight rem…

mistaken for yellow fever in regions where that disease … The fever is irregular, as a rule, varying greatly in … ing temperatures between 103° and 105° F. … others the temperature may be only slightly above … Hyperpyrexia occurs in rare instances.

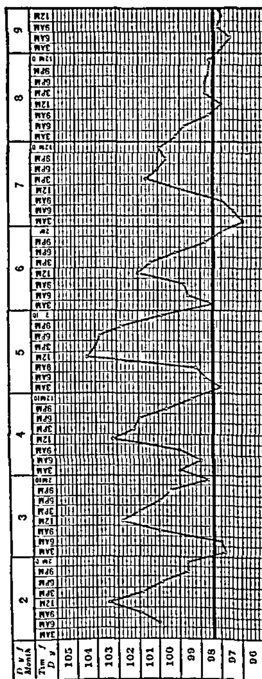


Fig 25 — Quotidian Falciparum Estivo Autumnal Malarial Fever

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and hiccough is a frequent symptom In untreated cases this form of malarial infection results fatally in the majority of instances death occurring through collapse but if properly treated the vast majority of patients will recover

Among the other forms of pernicious malaria in which the symptoms are most pronounced in the intestinal tract may be mentioned the *choleraic* form in which the symptoms so closely resemble those of typical cholera as to render a differential diagnosis through the clinical picture almost impossible without the aid of a blood examination the *gastralgic* form characterized by intense pain in the region of the stomach and the vomiting of blood stained material and the *dysenteric* form in which the symptoms are similar to those observed in acute infections with Endameba histolytica or infection with the dysentery group of bacilli

Other types of pernicious malaria are described in monographs upon the subject but are of such rare occurrence as to be of little practical importance

Combined and Multiple Malarial Infections

Infections with more than one species of malaria plasmodia are frequently encountered as are infections with more than one generation of the same species These combined and multiple infections often present very confusing clinical symptoms and render diagnosis most difficult In some instances one species of plasmodium will so greatly outnumber any other present as to color the clinical picture to such an extent that the infection with another species is not suspected and it is a common experience to discover such mixed infections through a blood examination On the other hand the presence of more than one species may alter the temperature curve so markedly as to render it so dissimilar from malaria that the infection is not even suspected although the patient may be dangerously ill The most common combination is infection with the tertian and sub tertian or estivo-autumnal plasmodia and often such infections unless quickly recognized may terminate in a pernicious attack Such combined malarial infections are always more dangerous than single infections and more resistant to treatment

Infections with more than one generation of the same plasmodium are of frequent occurrence and are of importance because the temperature curve in such cases is generally of quotidian character and apt to be mistaken for that of some other condition and the presence of malaria overlooked The writer has observed fatal cases of infection with two generations of *Plasmodium falciparum* considered as septic infection or some other condition because of the quotidian character of the temperature curve and the daily chills the malarial nature of the condition being unrecognized with the resulting death of the patients from pernicious malaria The symptoms in the types of malaria just noted are generally more severe than in single infections or infections with a

In fatal cases as the end approaches, the pulse becomes rapid irregular and weak the respirations shallow labored and irregular, and death occurs through collapse In some instances the temperature falls rapidly, accompanied by profuse perspiration and consciousness is regained but these favorable symptoms are followed by another paroxysm or even by a third, during which death occurs A few patients recover without treatment, but the vast majority of comatose pernicious infections are fatal if untreated The patients may live for only a few hours after coma develops or may linger for three or four days or even longer Albumin and hyaline and granular casts are frequently present in the urine, and during the attack the feces and urine are passed involuntarily or there may be retention of urine

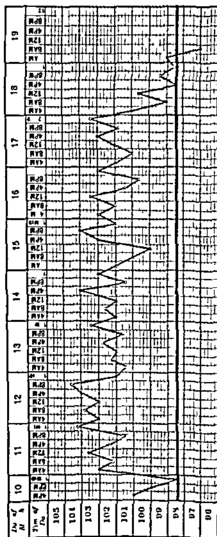


Fig 27 — Tertian Falciparum or Estivo Autumnal Malarial Fever Continuous temperature curve

Besides the comatose forms of pernicious malaria other forms have been described in which symptoms affecting the nervous system are prominent Among these may be mentioned the *amaurotic* form, the *delirious* form and the *hemiplegic* form The names indicate clearly the most prominent symptoms accompanying these infections

The so-called *bilious remittent fever* of the older writers is a commonly encountered form of estivo-autumnal infection in which pernicious symptoms often develop and end fatally This type of infection occurs in patients who have suffered for some time from malarial fever and who have not been treated or treated improperly The typical paroxysms disappear and the temperature becomes irregular remittent or continuous frequently resembling that of typhoid fever Marked mental symptoms develop such as delirium stupor or coma and the vomiting of bile stained fluid accompanied by severe pain in the stomach is often a persistent and prominent symptom Epistaxis or hematemesis is observed in some cases,

or 21 18 per cent showed plasmodia in the blood The rate of infection under twenty years of age was 23 56 per cent while the rate over twenty years of age was 19 22 per cent Of the 6 664 individuals showing plasmodia in their blood 3 761, or 55 09 per cent gave a history of a malarial attack within a year while 2 993 or 44 91 per cent gave a negative history for malaria

TABLE I

OCCURRENCE OF LATENT MALARIA AT CAMP STOTSENBERG ISLAND OF LUZON P I (CRAIG)

Age	*No Examined*	*No Infected*	*Percentage*
1 to 5 years	40	30	75
5 to 10 years	54	20	37
10 to 15 years	53	13	24 5
Over 15 years	45	28	62 2
Total	192	91	47 3

Table II compiled from the observations of others as well as my own gives a good composite picture of the incidence of latent malarial infections in most localities where the disease is endemic and anopheline mosquitoes are numerous

TABLE II

THE PREVALENCE OF LATENT MALARIA AT VARIOUS AGES

Age	*No Examined*	*No Infected*	*Percentage*
1 to 5 years	6 288	1,407	22 3
5 to 10 years	5 305	1 279	24 1
10 to 15 years	3 480	966	27 7
Adults	15 440	3 164	20 4
Total	30 513	6 816	20 4

It may be stated that about one fifth of the inhabitants of malarial regions carry the plasmodia around in their blood without having noticeable symptoms of the infection and that in many badly infested regions the percentage of latent infection in children runs close to 80 per cent and of adults close to 50 per cent

The percentage of latent cases that become carriers of malaria i e present gametocytes in the peripheral blood in sufficient numbers to infect mosquitoes varies considerably but in the writer s experience from 40 to 50 per cent of such cases become carriers of malaria and in badly infested regions the per centage is much higher

single generation of the plasmodia The falciparum infections are particularly prone to run an atypical temperature curve, because of either combined or multiple infections (see Figs 26 and 27), and many such cases have been confused with typhoid paratyphoid and other acute febrile conditions The most common type of irregular fever due to the causes mentioned or to insufficient treatment with quinine is a remittent or sub continuous type, in which the clinical symptoms are practically identical with those of a mild typhoid fever or with paratyphoid infection (see Fig 27) These types of fever were once known as typho-malarial fever, but their true nature is at once demonstrated by a blood examination It should never be forgotten that an examination of the blood for the malaria plasmodia should always be made in every febrile condition in malarial regions or in individuals coming from such localities and developing fever The neglect of such an examination is almost criminal with our present knowledge of the malarial infections

Latent Malarial Infections

In every malarial region a considerable number of the inhabitants harbor the plasmodia of malaria without symptoms of the infection being noted In discussing the pathology of malaria the fact has been mentioned that at the autopsy of patients dying from other diseases in whom no symptoms of malaria occurred before death the plasmodia were demonstrated in the spleen, and every stage in the human life cycle was found present These observations prove that the parasites may live in man for some time without producing symptoms, and such individuals are said to have a latent infection Such individuals frequently have gametocytes in their blood and are infective to mosquitoes so that these carriers of malaria are of immense importance in the transmission of the infection and their recognition essential in the prophylaxis of malaria

The percentage of latent infection among the inhabitants of malarial regions varies greatly in some regions only from 5 to 10 per cent showing infection, while in others as high as 60 to 80 per cent of individuals from one to ten years of age have been found infected

In 1906 the writer[23] investigated the occurrence of latent malaria in native Filipinos living in the barrios around Camp Stotsenberg which is located in one of the most malarial regions of the Island of Luzon P I Table I gives the results obtained in this survey

Table I as well as the observations of many students of malaria demonstrates that latent infection occurs in a large percentage of both children and adults living in malarial localities In the United States Bass[4] has published the results of a survey made in Mississippi in which the blood of 31,459 individuals was examined for the malaria plasmodia, of which number 6,664

valuable a microscopical examination of the blood is in the diagnosis of disease. In all of these cases the symptoms present were sufficiently typical of the disease diagnosed as to render the diagnosis justifiable and in all treatment with quinine resulted in the rapid disappearance of the symptoms.

The majority of the patients listed in Table IV were suffering from infection with *Plasmodium falciparum*, the estivo-autumnal plasmodium, a type of malarial infection *in which the symptoms are most apt to be atypical*. It is obvious that the recognition of these cases of latent and masked malarial fever is of the greatest importance, as in the latent infections we are thus able to prevent the development of symptoms by proper treatment and in many instances to prevent the development of gametocytes so that these patients do not become "carriers" of malaria, while in the masked cases we thus discover the true cause of the symptoms present and by specific treatment cure the infection.

TABLE IV

Diagnosis	*Number of Cases*
Anemia	20
Chronic dysentery	15
Typhoid fever	10
Chronic diarrhea	6
Pulmonary tuberculosis	5
Acute bronchitis	4
Insolation	6
Melancholia	4
Malta fever	6
Rheumatism, muscular	4
Neuralgia, facial	3
Pneumonia, lobar	3
Appendicitis, acute	2
Syphilis	2
Insanity	2
Peritonitis	1
Acute catarrhal jaundice	1
Cerebrospinal meningitis	1
Yellow fever	1
	96

The length of time during which a latent malarial infection may exist without producing symptoms is uncertain, but there is no doubt that it may be for several weeks or even months. The writer has observed numerous instances in which plasmodia could be demonstrated in the blood for from one to three weeks before symptoms developed and in one case of infection with *Plasmodium falciparum* for six weeks before a malarial paroxysm occurred. The masked cases may continue for weeks when the infection is not pernicious in character, or death may occur within a few days.

Masked Malarial Infections

Malarial infections, in which the symptoms are masked by those of a complicating disease or in which the symptoms closely resemble those of other diseases, are known as masked malarial infections

It frequently happens that a malarial infection is present, but the symptoms may be obscured by those of some other disease process, which is present at the same time Table III shows the clinical diagnosis in 91 cases of masked malaria in all of which the symptoms of the disease diagnosed masked those of the malaria that were present

TABLE III

Disease	*Number of Cases Masked*
Chronic dysentery	45
Chronic diarrhea	5
Pulmonary tuberculosis	18
Amebic dysentery	4
Acute bronchitis	2
Measles	3
Typhoid fever	2
Pneumonia	2
Gonorrhea	4
Rheumatism	1
Abscess of liver	1
Furunculosis	1
Diabetes mellitus	1
Cellulitis	1
Appendicitis	1
	91

Instances in which symptoms due to the malarial infection closely simulate those of other diseases are also common but as a rule the periodical nature of the symptoms will suggest their malarial origin Among the most common atypical symptoms of malaria which are often considered as due to some other disease may be mentioned various neuralgias periodical in type especially of the fifth nerve the intercostal nerves and of the occipital region, convulsions especially noted in malarial paroxysms in children various nervous conditions as insomnia delirium melancholia mania and vertigo while certain of the infectious diseases may be so closely simulated by malaria as to be almost indistinguishable especially typhoid pneumonia, yellow fever cerebrospinal meningitis and pulmonary tuberculosis

Table IV of ninety six cases of masked malaria in which the diagnosis as made before the malarial nature of the condition was discovered is given well illustrates how frequently malaria simulates other disease processes, and how

malarial infections and may be considered almost a symptom of the infection but a more severe type of acute bronchitis is a rather frequent complication of malaria which may persist for weeks after the malarial infection is cured and which often leads to a diagnosis of suspected pulmonary tuberculosis

Both lobular and lobar pneumonia occur as complications of malaria and until quite recently many observers believed that these conditions were caused by the malarial infection and that there was a distinct form of lobular or lobar pneumonia due to the malaria plasmodia While it is true that the localization of the plasmodia in the capillaries of the lungs may give rise to symptoms simulating pneumonia, there is no evidence that true lobular or lobar pneumonia can be produced by the plasmodia and it is now accepted that lobular and lobar pneumonia occurring in malaria are due to the usual organisms concerned in their etiology and not to the malaria plasmodia

Lobar pneumonia may develop suddenly or insidiously during an acute attack of malaria and the symptoms are usually rendered atypical by the occurrence of the malarial paroxysms In some instances the symptoms are like those occurring in a patient in whom no malarial infection is present but usually the course of the pneumonia is altered by the occurrence of chills and exacerbations of fever due to the malaria plasmodia The pneumonic symptoms may mask the malaria or vice versa The prognosis is always grave especially in the falciparum infections and the mortality is placed as high as 60 to 78 per cent by the Italian students of malaria Lobular pneumonia occurs less frequently as a complication of malaria but is closely simulated by congestion of the lungs caused by the presence of the plasmodia

Convalescence from pneumonia complicating malaria is usually slow often due to delayed resolution Empyema may occur but is very rare and of course due to complicating micro-organisms Fibrosis sometimes occurs and bronchiectasis may develop Pneumonic septicemia has been observed in falciparum infections and in patients in whom pneumonia has developed as a complication the pneumonia frequently terminates in delayed resolution a typhoid state or more rarely septicemia Pleurisy has been observed very infrequently as a complication of malarial infection

Tuberculosis was long supposed to be antagonistic to malaria and the older works upon malaria state that the two infections are seldom observed together As a matter of fact this statement is erroneous and one of the most common complications of malaria is tuberculosis It has also been observed that in patients suffering from tuberculosis a malarial infection will sometimes cause very acute symptoms followed by the development of miliary tubercles In the writer s experience the number of instances in which miliary tuberculosis was discovered at autopsy in patients dying of severe malarial infection supports the observation regarding the lighting up of miliary tuberculosis by malarial

Familial Malarial Infections

It is a common observation in malarious regions that, if one member of a family is suffering from an acute malarial attack, other members of the same family also will be found to be infected, if a microscopical examination be made of their blood, such infections being usually latent in character This is true because malaria is largely a ' house infection' and because infected mosquitoes harbor in human habitations for long periods of time and repeatedly bite the inmates For instance, the writer examined 10 Filipino families living in a barrio outside Camp Stotsenberg, Luzon, numbering 39 members in all, of which 26 were found to be infected with malaria plasmodia, and in one family of 5 members all were found infected One of the members of this family was suffering from an acute attack of vivax malaria, while the other 4 members had latent infections In this family there were 2 infections with *Plasmodium falciparum* 2 with *Plasmodium vivax* and 1 with *Plasmodium malariae* the only instance in the writer s experience in which all 3 of the common species of malaria plasmodia occurred in the same family at the same time

In view of the great frequency of familial malarial infections it should always be the practice to examine the blood of all members of a family, in which an acute case of malaria is occurring both because of the importance of treating latent infections and from a prophylactic standpoint

Complications of Malaria

Malaria like other infections may be complicated by other diseases a fact which often leads to confusing clinical pictures and errors in diagnosis Many of the symptoms noted in such complications have been laid erroneously at the door of malaria and some writers have even considered the complications as etiologically related to the malarial infection However, a typhoid fever or pneumonia complicating malaria does not differ in its etiology from the disease when occurring alone and the terms 'typho-malaria", "malarial pneumonia', etc should be abandoned

Nervous System —Of the diseases of the nervous system sometimes complicating malarial infection may be mentioned nervous prostration hysteria, acute mania paraplegia hemiplegia and meningitis Hysteria is a common complication in nervous women and even in men and the symptoms vary greatly in character and severity Mania paraplegia hemiplegia and meningitis are very rare complications and only occur in pernicious infections

Respiratory System —The most frequent complication in the respiratory system is acute bronchitis A mild type of bronchitis is observed in very many

malarial infections and may be considered almost a symptom of the infection but a more severe type of acute bronchitis is a rather frequent complication of malaria which may persist for weeks after the malarial infection is cured and which often leads to a diagnosis of suspected pulmonary tuberculosis

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Respiratory System — The most frequent complication in the respiratory system is acute bronchitis A mild type of bronchitis is observed in very many

malarial infection by quinine always resulted in marked improvement of the dysenteric condition

Acute and chronic gastritis may complicate malaria and often renders treatment by the oral administration of quinine very difficult owing to the irritability of the stomach

Acute Infections Complicating Malaria — Any of the acute infectious diseases may complicate malaria and lead to grave errors in diagnosis and treatment Among the most important may be mentioned typhoid fever paratyphoid fever and the eruptive fevers Typhoid fever sometimes complicates malaria and this complication has occurred in the writer s experience ten times in over five thousand cases of malaria observed Of these ten cases six were combined infections with falciparum malaria three with vivax malaria and one with quartan malaria The prognosis is always grave in these combined infections especially if the malarial infection is not promptly recognized and treated

Sequelae of Malaria

Owing to the profound effect of continued malarial infection upon the viscera and blood it is not surprising that numerous and serious sequelae are often observed following malaria However, it is not always easy to differentiate sequelae from complications for in many instances a certain morbid process will develop during an attack of malaria and it will be impossible to state whether or not it is the result of the malarial infection or is simply a complication of the disease In such instances we must depend upon a careful clinical survey of the case and the recorded experiences of others in deciding the question

The sequelae of malaria affect almost every organ in the body and also the blood and it will be convenient to consider them under the various systems

Nervous System — In the nervous system the sequelae are very largely due to the blocking of the capillaries of the brain by the plasmodia or their products such as pigment and their subsequent rupture but in part are undoubtedly due to the toxin or toxins produced by the plasmodia Sequelae in the nervous system are most frequent after falciparum infections and are frequently evanescent in character Psychical disturbances are sometimes noted as defective memory or periods of inattention or confusion Melancholia and mania have been observed and a condition of depression and lack of ambition is very frequently observed Observers have described aphasia hemiplegia and paraplegia after malarial attacks and a condition almost indistinguishable from multiple sclerosis has been described by several Italian observers

Affections of the peripheral nerves are frequently met with as sequelae of malaria Multiple neuritis has been noted by many observers and neuralgia is a very common sequela although not as common as is generally supposed

infection The writer has observed cases of pulmonary tuberculosis complicated by malaria in which at autopsy besides the occurrence of cavities and fibrosis there were present multitudes of miliary tubercles thus indicating that malarial infection may stimulate the formation of miliary tubercles Therefore, it is most important to recognize a malarial infection in tubercular subjects or the occurrence of tuberculosis in patients suffering from malaria

Circulatory System — Complications involving the circulatory system are observed frequently Any of the organic diseases of the heart may be present, and in severe estivo autumnal infections such complications may render the prognosis very grave While acute endocarditis may occur as a complication, it is most doubtful if it is ever due to the malaria plasmodia

Functional disorders of the heart are very common in malaria and a systolic murmur is noted frequently over the mitral area During convalescence a slow pulse is observed frequently

Genitourinary System — The most common complication in the genitourinary system is nephritis While albuminuria is very common it can hardly be called a complication as it occurs so frequently as a symptom of malaria or develops as a sequela of that infection Nephritis is often present together with malaria and when it occurs as a complication is usually of the sub acute or chronic type In rare instances a malarial infection occurring in a nephritic will cause the death of the patient due to the added congestion of the kidneys brought about by the malarial infection

Venereal disease often complicates malaria and gonorrhea orchitis epididymitis and the various stages of syphilis may be present coincident with a malarial infection In all of these conditions with the exception of syphilis the malarial infection markedly aggravates the symptoms and adversely influences the progress toward cure of the condition that may be present

Gastrointestinal System — In malarial regions in the tropics and sub tropics perhaps the most common complication of malaria occurring in the gastrointestinal tract is dysentery either amebic or bacillary in type, or some form of enteritis In such cases the malarial infection appears to aggravate the dysenteric or diarrheal condition The symptoms of malaria are often masked and diagnosis thus rendered difficult In certain instances the localization of malaria plasmodia in the mucous membrane of the intestine may give rise to symptoms of dysentery or diarrhea but such cases are not included in this discussion During the Philippine Insurrection many hundreds of our soldiers were returned to the United States from the Philippine Islands suffering from amebic dysentery or a chronic form of bacillary dysentery and a large proportion of such patients also suffered from malaria In these patients the presence of the malaria plasmodia undoubtedly aggravated the symptoms due to the infection with *Endameba histolytica* or the dysentery bacilli and the treatment of the

Orchitis and epididymitis have been described as sequelae of malaria but with insufficient evidence

Liver — In long continued cases of malarial infection a chronic form of hyper trophy of the liver occurs known as hypertrophic malarial hepatitis The condi tion does not cause much disturbance of function and no characteristic clinical symptoms are present It is doubtful if atrophic cirrhosis of the liver ever occurs as a sequela of malarial infection

Spleen — It has already been noted that enlargement of the spleen is almost invariably present in malaria and to this enlargement are due certain sequelae of interest and importance Rarely the enlarged spleen by its weight sinks into the abdominal cavity the ligaments supporting it become stretched and the organ may be felt as a movable mass through the abdominal walls This condi tion is known as wandering or floating spleen the symptoms being pain upon movement a feeling of weight in the abdomen and reflex disturbances as head ache nausea and vomiting

In acute or sub acute malarial infection the spleen may be very soft and friable and rarely this condition leads to rupture of the organ Rupture may be due to blows or falls retching in vomiting or to a sudden forcible movement of the body The writer has observed two instances of rupture of the spleen following malarial infection in both instances the symptoms being sharp lan cinating pain in the left side followed by collapse due to internal hemorrhage Death may occur very quickly or the patients may live for a day or longer depending upon the size of the laceration of the capsule of the organ and the amount of hemorrhage

Abscess of the spleen has been described as due to malarial infection but the few instances in the literature were undoubtedly due to pathogenic bacteria as the malaria plasmodia are not pyogenic organisms

Lymph Nodes — Enlargement of the lymph nodes has been described as a sequela of malaria but with insufficient evidence and it is not believed that it ever occurs as the result of malarial infection

Organs of Special Sense — *The Eye* — Among the sequelae of malaria noted in the eye may be mentioned amaurosis retino-choroiditis keratitis suppura tive choroiditis and paralysis of accommodation These sequelae are rare however and very few authentic cases have been reported

The Ear — Intermittent otalgia is sometimes present in chronic malarial infection and intermittent attacks of deafness have been reported by several observers It is probable that many such cases were really caused by large doses of quinine Labyrinthine vertigo occurs as a result of repeated malarial attacks in rare instances but is more common as a symptom of acute infection and in such cases treatment with quinine relieves the condition

The Blood — The sequelae observed in the blood after malaria consist of

Many of the cases of so-called "malarial neuralgia" have no connection with malaria, and the name is often used as a cloak for ignorance of the real etiology of the neuralgia present The regions most frequently affected with neuralgia due to malaria are the face and lumbar region Intercostal neuralgia is more rarely observed and sciatica very rarely

A persistent insomnia is often a sequela of malaria and is sometimes very resistant to treatment

Circulatory System — Malarial infection has but little effect upon the heart or blood vessels, so far as the production of definite lesions is concerned Although some authorities have described acute endocarditis and arteritis as sequelae of malaria, the proof is insufficient to establish their statements, and it is very doubtful if malaria ever leads to disease of the heart or blood vessels When such conditions occur during a malarial infection, they are complications rather than sequelae and due to some other cause

Digestive System — The localization of the plasmodia in the capillaries of the mucous membrane of the stomach and intestine may lead to sequelae of severe nature Acute gastritis and an acute or chronic ulcerative enteritis may follow malarial attacks and some authorities have described gastric ulcers following malaria A form of subacute or chronic dysentery may follow malaria, apparently due to the localization of the plasmodia in the mucous membrane and consequent destruction of the latter

Genitourinary System — The most common of the sequelae of malaria in the genitourinary system is albuminuria which is especially frequent after falciparum attacks While this condition is most often a complication of malaria it is true that sometimes a persistent albuminuria is noted after malarial infection and transient albuminuria is not infrequently encountered The writer s observations have led him to believe that albuminuria occurs at some time in at least 60 per cent of all falciparum infections and in from 25 to 30 per cent of vivax and quartan infections However, it does not persist after recovery from malaria in more than from one to five per cent of the severe falciparum infections

Nephritis occurs in some of the severe falciparum infections and in a very small proportion of vivax and quartan cases Either acute or chronic nephritis may occur as a sequela the most common forms being acute glomerular and chronic parenchymatous or interstitial nephritis The chronic forms are usually observed in patients who have suffered from repeated attacks of malaria and are in a cachetic condition Some form of nephritis is invariably present in all fatal malarial cases in the writer s experience

Polyuria is a frequent sequela of malaria usually transient in type but persistent in some cases The amount of urine passed may be enormous and lead to the suspicion of the presence of diabetes Glycosuria is probably never a sequela of malaria

portion of infections with all but *Plasmodium falciparum* Infections with the latter organism are eliminated quickly by proper treatment but vivax malaria especially is much more resistant and if certain strains of the plasmodium are involved will relapse repeatedly over long periods of time So frequent are relapses or recurrences in malarial infections that there is a prevalent belief that once a victim of malaria always a sufferer from the infection While this belief is erroneous recurrences do occur often for months and sometimes although rarely for years after the initial infection especially if proper treatment has not been administered

Time of Relapses or Recurrences

If the patient is residing in a malarial locality it is often impossible to ascertain the exact relapse periods owing to the chance of reinfection Celli as a basis for the computation of the time between relapses regarded every case of malaria that repeated itself in the infected individual from July of one year to the end of June of the next as a recurrence Of course this is a rule subject to great fallacy because of the chances of reinfection with the same species of plasmodium in malarial regions but it is probably as good a one as can be adopted under ordinary conditions

The writer [5] in 1909 published some observations upon the period of relapse in malaria which were very carefully checked by personal observations and which give a good idea of the usual periods between relapses in falciparum and vivax malarial fevers In a study of fifty five cases of falciparum malarial infection that relapsed it was found that the first relapse occurred at periods varying from ten to eighty days after the cessation of the symptoms of the primary attack The greatest number of relapses occurred between the twentieth and thirtieth days i e twenty three and almost as many between the thirtieth and fortieth days i e sixteen The earliest relapse was in ten days and the latest in eighty days after the primary attack In thirty six of these cases secondary relapses occurred and such relapses were usually at longer intervals than the primary relapses The earliest secondary relapse was fifteen days after the cessation of the symptoms of the primary relapse and the latest one hundred and fifty six days after the primary relapse

Fourteen of the fifty five cases studied had three relapses four had four relapses and two had five relapses of their infection

In eighteen cases of relapsing infection with the tertian plasmodium (*Plasmodium vivax*) studied by the writer all had one relapse ten had two relapses five had three relapses three had four relapses while no cases studied had five relapses In these tertian infections the primary relapse occurred between sixteen and forty-one days after the cessation of the symptoms of the primary at

secondary anemia, and in rare instances a form of pernicious anemia may develop The secondary anemia may be severe especially after estivo autumnal infections the erythrocyte count hovering around 2,000 000 cells per cu mm for weeks there being a proportionate decrease in leucocytes and hemoglobin In most instances this type of anemia is very amenable to treatment

In rare instances a form of pernicious anemia may develop after severe and long continued malarial infection in which the erythrocyte count may fall below 500 000 cells per cu mm and the blood picture of primary pernicious anemia, with the exception of nucleated erythrocytes may be present In these cases death may ensue, but recovery has been observed in some instances

Malarial Cachexia

In individuals who have suffered from repeated attacks of malaria, which have been untreated or improperly treated there develops a distinct clinical condition characterized by anemia and an enlarged spleen known as malarial cachexia This condition is most frequently observed in the tropics or sub tropics in regions where the falciparum malarial infections are prevalent, and it is especially apt to develop after latent or masked infections, which have been untreated because unrecognized

These chronic malarial infections are characterized by repeated attacks of fever atypical in character and the gradual development of anemia and an enlarged spleen Individuals suffering from this condition present a peculiar yellowish or grayish hue of the skin or an earthy pallor while the mucous membranes are pale and dry There is a loss of appetite diarrhea at intervals more or less emaciation and a condition of nervous exhaustion Between the febrile attacks the temperature may be normal but usually it is sub normal in the morning hours rising to 99° 100° or 101° F in the evening hours The spleen is generally considerably enlarged but is not painful on pressure The anemia present is of a secondary character the erythrocyte count averaging from ? 000 000 to 3 000 000 cells per cu mm

These individuals are very susceptible to other infections and even slight injuries are often attended by suppuration phlegmonous inflammation or hemorrhage

It should be remembered that individuals suffering from malarial cachexia seldom show many plasmodia in the blood even though fever may be present so that several preparations should be carefully examined before a negative result is accepted as definitely excluding this diagnosis

Relapses in Malaria

With but few exceptions untreated malarial infections will recur, and even treated infections will relapse when treatment is discontinued in a large pro

way that an accurate and scientific diagnosis can be made The symptomatology of the various forms of malarial infection is so often atypical or masked by other infections that a diagnosis based upon clinical symptoms alone is frequently impossible While typical cases of vivax malariae and falciparum malaria may be diagnosed by the classical symptoms present especially by the periodicity of the attacks and the character of the temperature curve many of these infections are atypical and it is only by a careful examination of the blood and the demonstration of the plasmodia in that fluid that the malarial nature of the condition present can be recognized

The importance of an examination of the blood in the diagnosis of malaria cannot be urged too strongly and every physician practicing in a malarial region should be qualified to recognize the common species of malaria plasmodia The plea so often heard that the busy practitioner has no time to make such an examination is very seldom true and when true is no excuse for neglecting a blood examination as it is possible in most localities to send blood smears to a local or state health department laboratory for examination

The writer has seen so much misery resulting from neglecting blood examination in fever cases occurring in malarial regions even the death of patients in some instances that he believes that in such regions a blood examination is absolutely essential in all fever cases and that the neglect of this procedure should constitute good grounds for a charge of malpractice

The blood may be examined in either unstained or stained preparations Prior to the development of good stains it was the practice to examine unstained blood preparations and to one well trained in recognizing the plasmodia in such preparations this method is still a valuable one However these organisms are more easily recognized in well stained preparations and today such preparations are universally employed

Examination of the Blood

The apparatus required for the examination of the blood for the malaria plasmodia is very simple requires little space and if necessary may be transported to the bedside of the patient and the examination made on the premises It consists of a compound microscope equipped with a one twelfth inch oil immersion lens a bottle of immersion oil microscopic slides and cover glasses two or three medicine droppers a bottle of Wright s stain a bottle of distilled water and a needle or blood lancet The ear lobe or finger is cleansed with soap and water or alcohol pricked with the needle and a small drop of blood secured upon a microscopic slide If the blood is examined fresh the drop should be near the center of the slide and should be covered at once with a cover glass and examined If the specimen is to be stained the drop of blood should be

tack the shortest period being sixteen days and the longest forty one days As in the infections with *Plasmodium falciparum* succeeding relapses tended to occur at longer intervals In some of the patients studied small doses of quinine were given irregularly which may have had some effect in delaying relapse, but it is not believed that the amount of the drug given could have influenced the result to any appreciable extent Long interval relapses are not infrequently observed Thayer (1897) instances the case of a physician who relapsed after an attack of vivax malaria 18 months before, while Schilling (1903) records 2 cases in which $8\frac{1}{2}$ months elapsed between the initial attack in 1 case and $2\frac{1}{2}$ years in the other The writer has observed several infections in which relapse occurred after periods of from 6 to 8 months and in which reinfection could be excluded

Etiology of Relapses in Malaria

It cannot be said that at present all authorities are agreed upon the cause of relapse in malaria The old theory of Schaudinn that relapses are due to parthenogenesis of the macrogametocytes remaining in the blood of the infected individual is now known to be erroneous and until recently the theory of Ross (1898) that relapses are due to the multiplication of schizonts remaining in the body and which have been unable because of the partial immunity to multiply in sufficient number to produce symptoms during the latent periods between the relapses has been the accepted explanation At the present time most authorities are inclined to believe that in the latent periods between relapses the plasmodia are undergoing cycles of development within the monocytes and reticulo-endothelial cells the so called exo erythrocytic cycle of development

In studying the question of relapse in malaria the utmost care must be used in ruling out reinfections and in regions where the infection is endemic and severe it is almost impossible to collect accurate data upon the subject, owing to the fact that all individuals are constantly exposed to reinfection The data given above was obtained from the study of infections in soldiers, who had been hospitalized and removed from malarial regions so that reinfection could be excluded definitely

Almost invariably the relapsing malarial patient is a carrier' of the infection his blood containing gametocytes capable of infecting suitable mosquitoes Thus the prevention of relapse in malaria is of vital importance and this question will be discussed in considering the prophylaxis and treatment of malaria

Diagnosis of Malaria

The diagnosis of malarial infection depends upon the demonstration of the malaria plasmodia in the blood of the suspected individual and it is only in this

is then washed in running distilled water and examined directly with a one twelfth oil immersion lens when dry A cover glass is not needed If it is desired to preserve the preparation the oil may be washed off with xylol and the prepara tion placed in a slide box in a dark place The final washing with distilled water is most important as this process removes the precipitate that forms during stain ing and greatly assists in differentiating the structure of the plasmodia

With the Wright stain the cytoplasm of the plasmodia stains a beautiful blue the chromatin of the nucleus a ruby red or dark red while the vesicular portion of the nucleus remains unstained The young schizonts or ring forms appear as blue rings having at some portion of the periphery a ruby red dot of chromatin or less frequently two such dots In the young gametocytes this dot of chromatin is situated within the ring The female gametocytes or macrogametocytes stain a much deeper blue than do the male gametocytes or microgametocytes and can be differentiated easily with this stain The various species of malaria plasmodia may be differentiated with little trouble in prepara tions stained with Wright s stain if attention be paid to the following distinctive features present in stained preparations

Differential Diagnostic Features of the Various Species of Malaria Plasmodia

Plasmodium vivax (Tertian Plasmodium) — 1 Larger size especially after the development of pigment Increased size of the infected erythrocyte and distortion in shape 3 Presence of Schuffner s dots (eosinophilic granules) in cytoplasm of infected erythrocyte 4 Number of segments or merozoites twelve to twenty four 5 Presence of all stages of human life cycle (schizog ony) in the peripheral blood 6 Schizogony completed in forty-eight hours 7 Gametocytes spherical in shape

Plasmodium malariae (Quartan Plasmodium) — 1 Medium size of plasmo- dium after development of pigment 2 No increase in size of the infected erythrocyte and no distortion in shape 3 Absence of Schüffner s dots in the cytoplasm of infected erythrocyte 4 Occurrence of the so-called band or ribbon forms' 5 Number of segments or merozoites six to twelve 6 Pres ence of all stages of schizogony in the peripheral blood 7 Schizogony com pleted in seventy two hours 8 Gametocytes spherical in shape

Plasmodium falciparum (Sub tertian Estivo-autumnal Plasmodium) — 1 Comparatively small size even when fully developed 2 Infected erythro- cyte generally slightly smaller than normal and never enlarged 3 Very small amount of pigment 4 Presence of basophilic granules (Maurer s dots) in cytoplasm of infected erythrocyte 5 Number of segments or merozoites ten to thirty 6 The segmenting forms fill only about two-thirds of the infected erythrocyte 7 Gametocytes crescentic in shape 8 Only the ring forms

collected upon one end of the glass slide, and as quickly as possible the end of another slide is brought in contact with it either before or behind the drop, and the blood allowed to spread along the applied edge As soon as this occurs, the applied slide is either pushed or drawn gently along the slide containing the drop of blood, and when this is properly done, a thin even smear of the blood is obtained The blood smear is then allowed to dry in the air and is ready for staining Most hematologists recommend cover glass rather than slide preparations (Editor)

Staining Methods — Many methods for staining the malaria plasmodia have been devised the best being modifications of the Romanowsky method The writer has always used the stain devised by Wright and known as Wright's stain For the best results one should prepare his own Wright's stain but there are some reliable preparations on the market The method of preparing the stain is as follows To a flask containing 100 c c of distilled water add 0 5 gm of sodium bicarbonate dissolve and then slowly add while shaking 1 gm of methylene blue heat in a steam sterilizer for one hour after the steam is up and then cool the solution A considerable amount of the methylene blue will remain undissolved but this should be allowed to remain in the solution

Make a solution of yellow aqueous eosin by adding 1 gm of the eosin to 1 000 c c of distilled water Add this solution slowly, while stirring to the cooled methylene blue solution which has been poured into a white dish or bowl The eosin solution is added until a well marked precipitate appears, and the surface of the mixture is covered with a greenish metallic scum Test repeatedly, while adding the eosin solution by placing a drop of the mixture upon a piece of filter paper When sufficient eosin solution has been added, a well marked pink halo should surround the small amount of precipitate upon the paper When this occurs allow the mixture to stand for fifteen minutes and then filter through one small filter paper the precipitate is saved, dried in a hot air oven at 60° C and the greenish powder so obtained is used in preparing the staining solution

The staining solution is prepared by adding 0 3 gm of the powdered precipitate to 100 c c of pure methyl alcohol Filter and add enough of the alcohol to bring up the entire amount to the original 100 c c The solution is now ready for use and should be stored in a dark cool place The stains used should be the best procurable

Method of Staining with Wright s Stain — An amount of the staining solution sufficient to cover well the blood smear is placed upon the microscopic slide or cover glass and is allowed to stand for from three to five minutes There is then added enough distilled water drop by drop to cause a distinct greenish metallic scum to form upon the surface of the mixture The stain is now allowed to act for from five to twenty minutes generally for five minutes, and the preparation

2 Allow the preparations to dry by leaving them in an incubator at a temperature of 37° C (98 6° F) for 1 to 1½ hours or in a covered slide box overnight

3 Dilute one part of a good Giemsa stain (this can be purchased already prepared) with six parts of neutral or slightly alkaline distilled water and place the smears in this mixture and leave for about ½ hour Previous fixation and dehemoglobinization are not necessary

4 Place the smears in distilled water for about 5 minutes for partial decolorization If the smears present a deep blue background and the leucocytes are almost black, they are overstained and worthless

5 Drain the smears thoroughly and allow to dry They are then ready for examination

If desired the Wright stain may be used instead of the Giemsa stains but it does not give as good results with the thick film method as does the latter It will be found that whatever method be employed in thick film staining for plasmodia a considerable amount of experience will be necessary with the method used before the malaria plasmodia may be easily differentiated from other objects which may be present in the preparations, and no one should attempt species differentiation in thick films who has not had proper instruction in such differentiation

The Field thick smear method is highly recommended by recent observers and will be found described in recent texts in clinical diagnoses

Objects which may be Mistaken for Plasmodia

In both thin and thick blood preparations there occur certain objects that may be easily mistaken for various stages in the development of the malaria plasmodia Space forbids a discussion of all such objects but it may be mentioned that the most commonly mistaken of all are the blood platelets and this mistake has been made frequently in the experience of the writer by well trained general pathologists who have not had experience in studying stained plasmodia It will be remembered that the cytoplasm of the blood platelet stains blue with the Wright and other similar stains while the chromatin granules collected in a more or less regular manner within the cytoplasm stains a bright pink or ruby red These chromatin granules occur as a collection of fine granules spherical in shape or irregular but never as a single large solid red dot as in the young gametocytes or ring forms of the malaria plasmodia Sometimes blood platelets occur in crescent shaped masses and may then be mistaken by the tyro for the crescentic gametocytes of *Plasmodium falciparum* while in other instances irregular masses of blood platelets may be superimposed upon a red blood corpuscle and be mistaken for schizonts but the absence of pigment should serve to differentiate such forms The most frequent mistake is to consider a single blood platelet super

very young pigmented forms and gametocytes usually occur in the peripheral blood 9 Schizogony completed in forty-eight hours approximately

Plasmodium falciparum quotidianum (Quotidian Estivo autumnal Plasmodium) — 1 Very minute size, much smaller than *Plasmodium falciparum* Some of the "ring forms" are so small as to be almost indistinguishable 2 Infected erythrocyte smaller than normal, often crenated and distorted in shape 3 Smaller amount of pigment than in any other plasmodium of man, often consisting of a single granule or minute collection of granules 4 Basophilic granulation of infected erythrocyte sometimes present 5 Number of segments or merozoites six to eighteen 6 Only "ring forms", very small pigmented forms and gametocytes present in the peripheral blood 7 Gametocytes crescentic in shape and smaller than those of *Plasmodium falciparum* 8 The segmenting forms fill only about one half of the infected erythrocyte 9 Schizogony is completed in twenty four hours

Plasmodium ovale — 1 Medium size, slightly larger than *P malariae* 2 Infected erythrocyte slightly larger than normal, usually oval in shape with ragged frayed out periphery 3 Presence of Schuffner's dots (eosinophilic granules) even in cells containing the "ring forms" 4 Number of segments or merozoites six to twelve usually eight 5 Presence of all stages of the human life-cycle (schizogony) in the peripheral blood 6 Schizogony completed in forty eight hours 7 Gametocytes spherical in shape

Thick Film Method

In a large majority of malarial infections the examination of one or more blood smears prepared and stained in the manner already described will result in the demonstration of the plasmodia if present, but in many latent infections and in falciparum malaria in which the plasmodia often are few in the peripheral blood the use of thick stained blood preparations is absolutely necessary This is especially true in making malaria surveys when it is desired to ascertain the percentage of inhabitants in certain regions showing plasmodia in their peripheral blood or in the examination of individuals, who have become infected during periods of latency when plasmodia are very few in the peripheral blood and cannot be demonstrated in ordinary stained preparations

Many methods of staining thick blood films for the malaria plasmodia have been devised, but the writer has found that the one described by Barber and Komp to be more generally satisfactory than other methods that he has employed The technic is as follows

1 Collect large drops of the patient's blood upon carefully cleaned microscopic slides and smear with a needle over an area about half that covered by an ordinary thin blood smear

2 Allow the preparations to dry by leaving them in an incubator at a temperature of 37° C (98 6° F) for 1 to 1½ hours or in a covered slide box overnight

3 Dilute one part of a good Giemsa stain (this can be purchased already prepared) with six parts of neutral or slightly alkaline distilled water and place the smears in this mixture and leave for about ½ hour Previous fixation and dehemoglobinization are not necessary

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imposed upon a red blood corpuscle for a young gametocyte or ring form of the malaria plasmodia but if one remembers that in such stages of development the chromatin in the plasmodia is always in the form of a solidly stained red dot, while the chromatin of the blood platelet is always in the form of a diffuse collection of tiny grains, staining less intensely, this error can be easily avoided

Serological Tests in Diagnosis of Malaria

There have been several attempts made to devise a serological test that would be valuable in the diagnosis of malarial infection Complement fixation so far apparently has been most valuable in this respect and the observations of Thomson (1918-1919) Kingsbury (1927) and Coggeshall and Eaton (1938)[15] have shown that complement fixing substances are present in the blood of patients suffering from malaria and may be demonstrated by a complement fixation test The test perfected by Coggeshall and Eaton has given the best results to date, but it is still in the experimental stage of development

Taliaferro and Fisher (1927-1928) were able to demonstrate that precipitins occurred in the blood of individuals suffering from malaria using an antigen prepared from placental tissue rich in plasmodia but this test proved unreliable in diagnosis The test devised by Henry (1927), known as the 'melanoflocculation test based upon the supposition that malaria pigment (melanin) is an active substance capable of giving rise to specific antibodies in the blood serum of malarial patients has been found to be a non specific test and positive reactions with it are only suggestive of the presence of malarial infection The test of Proske and Watson (1939) which is a colorimetric one gives a high percentage of positive results in malaria but is not specific although its authors believe that its much higher sensitivity in malarial infections may render it of definite value in diagnosis

Clinical Differential Diagnosis of Malarial Infections

The diagnosis of the various types of malarial fever and their differentiation from other infections or diseases is most accurately and promptly accomplished by a microscopical examination of the blood As already stated many malarial infections present such atypical symptoms that diagnosis must depend upon the results of a blood examination and in falciparum infections diagnosis based upon the clinical symptoms that may be present is especially difficult and in these infections the neglect of a blood examination has more than once in the writer's experience led to a fatal result because the malarial nature of the condition present was overlooked

While a blood examination should always be made in every case of fever occurring in malarial regions or in patients coming from such regions it is sometimes impossible to make such an examination and in such instances we must depend upon the symptoms present in order to differentiate malaria from other infections or diseases which may be present Among the diseases with which malaria is often confused or vice versa may be mentioned the following

Cerebral Apoplexy —Falciparum infections in which coma develops suddenly are very apt to be mistaken for cerebral apoplexy The differential diagnosis between these forms of malaria and the latter condition is often impossible without a blood examination The high temperature in comatose malaria when present is a differential feature of importance and the presence of splenic enlargement and a history of previous attacks of malaria are also of assistance in the differential diagnosis

Dysentery —As already stated malarial infections are often associated with symptoms suggestive of bacillary or endamebic dysentery and are frequently complicated by these infections A microscopical examination of the blood and of the stools should serve to differentiate malaria and endamebic dysentery while proper bacteriological examinations will differentiate the bacillary forms of dysentery

Hepatic Abscess —Owing to the febrile condition present in most cases of abscess of the liver whether due to *Endameba histolytica* or bacteria this condition is frequently confounded with malaria The enlargement of the liver with tenderness on pressure and the lack of enlargement of the spleen point conclusively to hepatic abscess However a blood examination for the malarial plasmodia and a white count to determine whether or not a leucocytosis is present should demonstrate the true nature of the condition

Relapsing Fever —Sub-continued and remittent forms of malarial fever may be easily confused with relapsing fever in regions where both infections occur The peculiar periodicity of relapsing fever should distinguish it from malaria but a microscopical examination of the blood is the most decisive method of differentiating these two infections

Typhoid Fever —There is probably no disease which has been so frequently confused with malarial infections as typhoid fever During our war with Spain practically two-thirds of the cases of fever occurring at Chickamauga Park and other camps were at first diagnosed as remittent malarial fever and it was not until the Widal test was applied and the blood carefully examined microscopically that this mistake in diagnosis was corrected The symptoms of typhoid fever and some cases of falciparum malaria are very similar and a differential diagnosis from clinical symptoms alone is often impossible However if the disease is malaria the administration of from thirty to forty grains (2 to 2 6 grms) of quinine per day for several days will result in a fall in the temperature

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Tuberculosis — Many cases of tuberculosis running a daily temperature are considered as malarial in nature especially where the latter infection is endemic The two conditions can be easily distinguished by a blood examination and a bacteriological examination of the sputum for the tubercle bacillus

Yellow Fever — Where both yellow fever and severe forms of malarial infection are endemic or epidemic, the differentiation of the two conditions is often impossible from the clinical symptoms that may be present That form of malarial infection known as bilious remittent fever", is especially apt to be mistaken for yellow fever by those who are not expert in the recognition of either infection As examination of the blood for the malaria plasmodia is often the only way in which a differential diagnosis can be made in some of these cases, it should always be insisted upon whenever there is any suspicion that yellow fever is present in a malarial locality

A large number of other disease conditions and infections have been confused with malarial infection, but it would merely be repetition to consider them in detail The important point to remember in making a differential diagnosis of malaria is the absolute necessity of blood examinations if such a diagnosis is to be of any scientific value for data based upon clinical symptoms are notoriously misleading and should receive little credence, where the differential diagnosis of malarial infection is concerned

Prognosis of Malarial Infections

In vivax and malarear malarial infections the prognosis, so far as danger to life is concerned is excellent While a few fatal cases of infection with these plasmodia have been recorded they are so exceptional as to be of no practical importance as regards the general prognosis of such infections

However in falciparum infections the prognosis should always be guarded for while the vast majority of such infections do not prove fatal the death rate from these forms of malaria is very high in regions where they are prevalent Prognosis is greatly influenced in these infections by local conditions as regards the liability to repeated infection the economic status of the patient and the presence of complicating disease processes In the poor the prognosis is not as

favorable as in the rich nor is it as favorable in those, who have been exhausted by repeated attacks of malaria or by some other infection as in those who have been in robust health prior to the attack of malaria In the pernicious forms of falciparum infection the prognosis is always very grave especially if treatment is not administered promptly and of the various forms of pernicious malaria the most fatal are the cerebral and algid forms and the rare pneumonic form It should not be forgotten that despite the most strenuous treatment some cases of pernicious malaria will prove fatal, so that the prognosis is always grave and the physician should be very guarded in expressing an opinion in these cases as to ultimate recovery The experience of English surgeons with falciparum malaria occurring in British troops in Macedonia during World War I has emphasized the gravity of the prognosis in these types of malaria for they lost a considerable percentage of their cases of pernicious malaria even when the most approved methods of quinine therapy were instituted promptly

In estimating the prognosis in malarial infections it may be stated that it is always favorable as to recovery from an acute attack in all forms except that caused by *Plasmodium falciparum* but a guarded prognosis should be given as to the actual elimination of any malarial infection as even with the best treatment relapses are common and the infection may persist for many months Some authorities go so far as to state that treatment of any kind is merely suppressive and that the actual elimination of the infection depends upon a gradually acquired immunity but this conception would appear to be erroneous for if any drug employed in treatment is able to suppress symptoms it follows that a certain number of plasmodia must be destroyed by it and the continued use of such a drug must result eventually in the destruction of all the plasmodia The writer's experience with long continued treatment with quinine in proper dosage has convinced him that such treatment does eliminate malarial infection and is not purely suppressive in character and the same probably is true of quinacrine hydrochloride (atabrine)

The prognosis of complicated malarial infections is that of the particular type of malaria present plus that of the complication and is always more grave than in uncomplicated infections The prognosis of sequelae usually is good unless lesions have occurred that would prevent recovery

Prophylaxis of Malarial Infections

It is unnecessary to call attention to the very great importance of the prophylaxis of malaria in all regions where these infections exist for it is a self evident fact to anyone who has studied the effect of malarial infection upon the growth and development of nations that it is one of the greatest factors in the underdevelopment economically physically mentally and morally of the peoples

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In smaller collections of water an ordinary watering can may be used or the oil may be poured from a bucket or dipper into the water and allowed to spread Care should be taken that the oil covers every portion of the water and inspections should be made at frequent intervals to see that aquatic animals or currents of air have not displaced the film The oil should be renewed every two or three weeks or oftener if local conditions render it necessary Usually half an ounce of oil per square yard of surface to be covered will be found sufficient and it is good practice to inspect every week and renew the oil if necessary

In running water the use of the drip barrel filled with the oil is valuable the drip being carefully regulated The larvicide used in the Canal Zone a mixture of crude carbolic acid rosin and caustic soda has been found very efficient, killing the larvae within five minutes

The destruction of mosquito larvae by fish is of service under certain conditions Certain species of fish are voracious feeders upon mosquito larvae and stocking ponds lakes or slowly running water with such species has proven efficient in many instances in destroying the larvae The species most useful are the roach carp top minnows and gold fish This is a method that can be used to advantage in keeping fountains ornamental pools or small ponds free from mosquito larvae The use of Paris green one part to one hundred parts of sand distributed by spray is a very efficient larvicide and success has attended its use when sprayed from aeroplanes over large surfaces which could not be oiled

Some mosquitoes transmitting malaria breed well in small collections of water and the destruction of such breeding places is most important Among the most common small breeding places may be mentioned uncovered fire buckets choked rain gutters on roofs unused hoppers in to lets tubs empty tin cans unscreened water tanks and depressions left in the ground by the hoofs of domestic animals The discovery of such breeding places and their removal or protection from mosquitoes are of vital importance in the prophylaxis of malaria as they are all located in close proximity to human habitations where the species of mosquitoes transmitting malaria prefer to breed

The recent introduction of the powerful insecticide DDT (dichloro-diphenyl trichloroethane) has placed in our hands the most useful agent of this nature so far discovered It is especially effective against every stage in the development of mosquitoes except the eggs and contact with it in solutions quickly kills the adult mosquitoes Its application to surfaces in the form of sprays has a lasting effect as insects alighting on or crawling across such surfaces will be killed after weeks and even months have elapsed since the original spraying It is far superior to petroleum and other agents when applied to small containers as water barrels etc. where mosquitoes may breed and has a prolonged residual effect but in natural collection of water the residual effect is much less and in some situations of little importance Because of its powerful action DDT should be employed

suffering from its ravages Aside from the toll in deaths which, in some endemic regions far exceeds that from any other disease, it is a demonstrated truth that people suffering from repeated malarial infection can never hope to compete in industrial development with those free from infection, owing to the physical and mental damage inevitably caused by malaria

In prophylaxis the following measures have been found of practical value (1) The destruction of mosquitoes transmitting malaria (2) The protection of man from the bites of mosquitoes (3) The destruction of the malaria plasmodia in man It will thus be seen that prophylaxis is divided into two classes of methods those based upon the rendering harmless of the mosquito transmitter and those based upon rendering harmless the human transmitter for even as the mosquito transmits malaria to man, so man transmits the infection to the mosquito

Destruction of Mosquitoes Transmitting Malaria

The ideal method of prophylaxis in malaria is the destruction of the mosquitoes transmitting the infection but this is sometimes impossible, so that it is necessary to rely upon other methods The destruction of the mosquito is best accomplished before these insects reach adult life, and this is done by the destruction of their breeding places or of the immature forms of the insects

The destruction of the breeding places of mosquitoes is accomplished by drainage and filling in of the land in which water collects and forms good breeding places for these insects These measures can be applied over a large extent of territory and instances are on record in which these measures alone have resulted in the disappearance of malaria from certain localities, but in the majority of cases all known prophylactic methods should be combined in our fight against these infections The methods to be employed in the destruction of the breeding places of mosquitoes as drainage filling in and the removal of shelter are subjects pertaining to sanitary engineering and will not be considered here

The destruction of the larvae of mosquitoes transmitting malaria is of great importance in prophylaxis and the substances employed for this purpose are petroleum phinotas oil sulfate of copper Paris green and a combination of crude carbolic acid rosin and caustic soda The most generally useful substance is petroleum which acts by coating the surface of the water with a layer of oil which prevents the larvae from breathing at the surface or gets into the breathing apparatus and thus prevents breathing An oil should be selected that will spread in a thin even layer, and experience has shown that the grade of petroleum known as light fuel oil is most satisfactory while a thicker oil composed of four parts of oil of eighteen gravity and one part of oil of thirty four gravity is also excellent for this purpose The application of the oil to large bodies of water is best made with a hand pump having a straight nozzle

region should be ascertained and the species mostly concerned in transmission identified If this is done much expense may be saved as it may thus be possible to eliminate the breeding places of this particular species instead of spending time and money in trying to abolish the breeding places of all species of anopheles that may be present in the locality

Of the methods that are now available for preventing the breeding of mosquitoes and killing the adult insects the most valuable are the following in order of importance drainage and elimination of the breeding places chemical treatment with DDT or other reliable insecticide of breeding places that cannot be eliminated and the killing of the adult mosquitoes by the use of DDT or other insecticide if DDT is not available or cannot be employed for any reason As already stated usually it will be found necessary to use more than one method in many localities to secure the best results

Protection of Man from Bites of Mosquitoes

When it is impossible to get rid of all mosquitoes transmitting malaria in any locality by the destruction of their breeding places or their larvae the protection of the inhabitants from the bites of these insects is a prophylactic measure of great value and one which should be combined always with other prophylactic measures if necessary and in almost every malarial region it is necessary

The protection of man from the bites of mosquitoes may be accomplished by screening of human habitations the use of DDT in killing the mosquitoes in dwellings the employment of mosquito nets and bars and the use of various odorous substances which repel these insects

The screening of human habitations is of prime importance The screening material used should be copper screens or well painted iron screens with no 18 mesh i e containing 18 meshes to the linear inch After installation in windows and doors all screens should be carefully inspected at frequent intervals to insure their efficiency Window screens should be placed outside the window sashes very carefully fitted and the entire window should be covered by a single screen which may be detached or opened if necessary Double screen doors should be employed for out side doors and should open outward

The use of mosquito bed nets should always be insisted upon in malarial localities unless the habitation is carefully screened If bed nets are used they should be tucked in under the mattress at night and during the day should be either folded over the top of the net suspended on the upright or tucked in under the mattress after the bed is made Careful inspections of the net should be made frequently for holes which might admit mosquitoes

Head nets and gloves are useful and indispensable in some localities where mosquitoes are numerous and it is necessary to be out of doors at times when

for treating all collections of water, in which mosquitoes are breeding and it may be used as a dusting powder or in oily solutions in the various ways in which petroleum mixtures have been used in the past The knapsack spray pump and the aerosol dispenser are most useful in treating small collections of water and in spraying rooms for the purpose of killing adult mosquitoes

DDT is a toxic substance, and when handled in some ways careful precautions should be taken to avoid poisoning Contamination of food with this substance must be guarded against and if oily solutions are being used care should be taken that it is not absorbed through the skin so that contamination of the skin and garments should be avoided Casual contact with oily solutions of DDT are not followed by harmful effects, but prolonged contact may be harmful Continued inhalation of oil or kerosene mixtures of DDT in 5 per cent or stronger solutions may be followed by toxic symptoms and under such circumstances a suitable respirator should be employed If DDT is used in powder form precautions should be taken that it does not contaminate food products as toxic symptoms follow ingestion of this substance more rapidly and are more severe than when it is inhaled Respirators should be worn, if one is handling large amounts of DDT in powder form in order to avoid the dust from this substance when it is being used

While usually under normal conditions DDT may be employed safely it does produce toxic symptoms when ingested or by absorption of DDT solutions through the skin or respiratory tract The toxic symptoms produced in laboratory animals are nervousness and hyperexcitability loss of appetite trembling and convulsions Dysfunction of the liver and kidneys may precede the nervous system manifestations and animals dying of DDT poisoning present a toxic necrosis of these organs

So far as is known by the writer there have been no cases of severe toxic symptoms occurring in those handling DDT and when one considers how many thousands have been and are handling this substance constantly it would appear that while DDT is toxic a very marked resistance to its toxicity must exist in man In the United States Army where DDT was first employed and has been employed for many months the most careful neurological physical and laboratory examinations have failed to show any variation from normal in soldiers who have handled this substance over long periods of time While this is true it is the part of wisdom to use the precautions above mentioned when employing it in the prevention of mosquito breeding or in killing adult mosquitoes

The most valuable methods of prophylaxis in malaria are those directed toward the destruction of the larvae of transmitting mosquitoes and the elimination of the breeding places of these insects The destruction of the adult mosquitoes also is most valuable and before employing the methods which are effective for this purpose the particular species of mosquito present in the suspected malarial

and culicines tested Other repellents are indalone and Rutger s 612 Both of these give protection for over 2 hours after being applied

Destruction of Plasmodia in Man

It is obvious that if it were possible to destroy the malaria plasmodia immediately after inoculation by the mosquito infection would not occur and that such a method would be of inestimable value in the prophylaxis of these infections While at the present time we have no drug that is capable of killing the sporozoites of the plasmodia inoculated by transmitting mosquitoes it has been demonstrated that both quinine and atabrine are capable of killing trophozoites and preventing the occurrence of symptoms This so-called suppressive treatment has proven of immense value to our armies operating in malarial regions by keeping troops already infected in a condition fit for combat and thus preventing a break-down in military operations The subject of *quinine prophylaxis* has been more fully discussed perhaps than any other subject in the realm of preventive medicine and there are many different opinions regarding the value of the drug in preventing malaria It would be useless to enter this controversy at the present time but it may be stated that quinine administered in sufficient dosage will prevent the occurrence of symptoms of malaria and if its use is persisted in will eradicate malarial infection Until quite recently it was believed that quinine would kill the sporozoites of the malaria plasmodia when inoculated into man by the mosquito and thus prevent infection but the recent experiments of Yorke and Macfie[3] upon the production of malaria in paretics by the bites of infected mosquitoes apparently demonstrate that the drug does not kill the sporozoites and therefore cannot prevent malarial infection However these investigators have also shown that if the quinine be continued after the mosquitoes had bitten even though the sporozoites were not destroyed symptoms of malaria did not develop thus indicating that the drug destroyed the schizonts which developed from the sporozoites and thus the infection was eradicated The experiments of Yorke and Macfie are confirmed by practical experience in the field for it has been shown repeatedly that troops operating in malarial localities show few cases of malaria as long as proper amounts of quinine are being taken but after their return to non malarial localities or to carefully sanitated posts and if the quinine is discontinued within two weeks many cases of malarial infection occur If the quinine be continued for several weeks very few cases of malaria will develop

These observations demonstrate in the writer s opinion that while the administration of quinine as a prophylactic measure will not prevent actual infection with the plasmodia it will prevent the development of symptoms in most individuals and if taken continually for several weeks after exposure will eradi

insects are biting A good head net and gloves should always form part of the equipment of travelers in malarial regions and should be a part of the equipment of troops serving in such regions for the use of guards and night patrols

The screening of patients suffering from malaria is a prophylactic measure of very great value As it is often impossible to be sure whether gametocytes are present or absent it is best to screen every malarial patient, either by placing them in carefully screened rooms or by use of the bed net By so doing we not only protect the patient from possible reinfection through the bites of infected mosquitoes but still more important, we protect mosquitoes from acquiring the plasmodia from the patient and thus becoming transmitters of the infection to healthy individuals in the locality Patients whose blood contains plasmodia, should be screened until the blood is free from the parasites or if gametocytes be present until their number has been reduced to a non infectious minimum i e to less than one per 500 leucocytes In treating patients with general paralysis by inoculation with malaria these patients need to be screened as described above

One of the most important of all methods of protecting man from the bites of mosquitoes is the spraying of the ceilings walls screens and contents of rooms in barracks and dwelling houses with solutions of DDT Such spraying renders the sprayed surfaces lethal to both mosquitoes and flies that walk over or alight upon them For this purpose the so-called residual spray" of DDT should be used, and this consists of 5 per cent of DDT, 15 per cent methylated naphthalene and 80 per cent kerosene It is applied by means of a spraying apparatus and to screens and other surfaces not suitable for spraying by means of a paint brush The amount of the spray to be used is 1 quart of 5 per cent spray to 250 square feet of surface and enough should be used to moisten the surface but there should be no run-off If spraying is done carefully, one application has been found to be effective for 3 months It should be remembered that DDT does not repel mosquitoes but kills them by contact, and death of the mosquito usually occurs in an hour after such contact

A prophylactic method of much less value than either screening or the use of the DDT residual spray is the smearing of substances upon the skin that are known to be mosquito repellents For this purpose various chemicals have been used as oils of eucalyptus citronella pennyroyal and anise camphor, vaseline and kerosene A mixture consisting of one part of oil of citronella and six parts of liquid vaseline has been largely used and the United States Army has developed a repellent which is said to be much more effective than any so far recommended but its composition has not been published It is officially known as the 6-2-2 repellent and has been found to give efficient protection from bites for as long as three and a half hours against certain species of anopheles and applied every - hours to the skin it protected from the bites of all anophelines

following the first few doses but usually even such mild symptoms are not noted In rare instances atabrine has to be discontinued because of toxic symptoms as severe nausea and vomiting diarrhea abdominal pain or nervous manifestations as hyperexcitability and severe headache Recently it has been noted that in rare instances atabrine appears to activate a form of lichen eruption when taken for long periods of time In most individuals a yellowish discoloration of the skin and conjunctivae appears after several days following administration but this is not due to any action upon the liver but is due to the deposit of the drug in the skin and disappears within a few weeks following cessation of treatment In some cases pigmentation of the tonsils and subungual tissues has been described

Treatment of Malarial Infections

The comparatively recent discovery of new drugs that are useful in the treatment of malarial infections has rendered the modern therapy of these conditions quite different from that given when we possessed only quinine for this purpose At the present time we have three drugs that are almost specific in the treatment of malaria i e quinine atabrine and plasmochin and these will be discussed separately together with the indications for their respective employment in treatment

Quinine

The proper use of quinine in the treatment of malarial infections throughout the world has demonstrated that it is a specific and the writer s experience has convinced him that this is true and none of the recent adverse reports upon the efficiency of quinine in the treatment of malaria has shaken in the least his belief that in quinine we possess a true specific in the treatment of these infections

That quinine and its salts produce the death of the malaria plasmodia in solutions of the strength usually produced in the blood by therapeutic doses is easily proved by adding such solutions to blood containing the plasmodia under the microscope In addition the study by staining methods of blood containing the plasmodia from patients under treatment with quinine conclusively proves that the drug is capable of killing the plasmodia as shown by the staining reactions obtained Marked degeneration of the cytoplasm of the plasmodia occurs after the exhibition of quinine and fragmentation and prevention of normal sporulation follow therapeutic doses The effects of quinine are most marked upon the schizonts but even the gametocytes during the earlier stages of development may be killed by proper amounts of the drug

Quinine is most efficient during the early stages of the development of the schizont but is capable of killing the plasmodia up to the presporulating stage

cate the infection The method is then broadly speaking a prophylactic method and accomplishes the same result in the end not by preventing infection by killing the sporozoites but by preventing the occurrence of symptoms of the infection by eradicating the schizonts produced from the sporozoites In most malarial regions it will be found necessary to combine with the prophylactic methods already mentioned the suppressive use of either quinine or atabrine, and this is especially true in the case of troops operating in such regions or where any large body of men are collected in a malarious locality The reader is referred to the paper by McNabb and Stewart[30], which so well illustrates the value of quinine as a suppressive measure in troops serving in the Canal Zone

The exact dose of quinine to be employed in suppressive treatment is still a matter of controversy some authorities preferring small daily doses while others prefer larger doses administered daily or at longer intervals In the opinion of the writer the daily dose should never be smaller than 0 65 gm (gr 10) or larger than 1 gm (gr 15) preferably administered at night Quinine should be given in capsules or in solution when so employed and the utmost care should be taken to see that it is actually swallowed as many individuals object to its use in this manner especially of soldiers The entire dose may be taken late in the evening or half of the dose in the morning and the remainder in the evening

At the present time *atabrine* (quinacrine hydrochloride) is the drug of choice for use in suppressing symptoms of malarial infection and our experience with it in our troops serving in malarious regions during World War II has demonstrated beyond all question its superiority over quinine in this respect As in the case of quinine it does not kill the sporozoites inoculated by the mosquitoes but it does destroy trophozoites and schizonts and thus prevents the development of symptoms Apparently it is more powerful in this respect than is quinine is better tolerated by the individual and while it does not prevent malarial infection, it will suppress symptoms for long periods of time, if taken in daily doses as recommended

It has been found that larger doses of atabrine can be given in suppressive treatment than was thought possible when it was first introduced and the experience of our armies in the use of the drug in this manner has proven that toxic symptoms very rarely occur with the larger doses, and that the results obtained are much better than with those previously recommended At the present time the dosage recommended by the Office of the Surgeon General of the Army is one tablet of atabrine 0 1 gm (gr 1½) daily at the morning or evening meal or a total of 0 7 gm per week Under extraordinary circumstances this dose may be increased for short periods to two tablets daily The ordinary dose may be continued indefinitely if necessary

The suppressive use of atabrine is not followed by unpleasant or toxic symptoms except in comparatively rare instances Some individuals have slight nausea

practically impossible to lay down any hard and fast rule regarding the dosage of quinine in malaria and the author believes that it is preferable to judge each case on its own merits and administer the drug in accordance with the severity of the symptoms which may be present

However a few words should be said regarding the overdosing with quinine so frequently observed even in simple vivax malaria The writer has frequently seen from 5 to 6 gm (75 to 90 grains) of quinine administered during twenty four hours in benign vivax attacks and it is exceedingly common to observe the administration of 4 gm (60 grains) of the drug a day in many malarial localities Such large doses of quinine are very seldom if ever required in order to overcome a malarial infection and if as is usually the case the drug is administered by mouth in such doses without the appearance of symptoms of cinchonism it proves that it is not absorbed from the stomach and some other method of administration should be resorted to If this is done it will be found that much smaller doses will cause the disappearance of clinical symptoms As a rule in the treatment of acute attacks of tertian and quartan fever it is seldom necessary to administer more than 2 gm (30 grains) of quinine in divided doses during twenty four hours while in estivo autumnal infections 2 5 to 3 gm (40 to 45 grains) of quinine in divided doses during twenty four hours are generally sufficient Of course these amounts of the drug should be continued daily until symptoms have disappeared

The method of administration of quinine will vary with the severity and type of infection which may be present Quinine may be administered by mouth by rectum subcutaneously intramuscularly or intravenously and the method adopted should vary with the condition of the patient and the type of infection

In the vast majority of acute and chronic malarial infections quinine should be administered by mouth and the sulfate is the salt generally employed In practically all tertian and quartan infections and the majority of estivo autumnal infections the oral administration of quinine will accomplish all that is desired and the advocacy of the subcutaneous and intramuscular administration of the drug by some recent writers in ordinary malarial infections should not receive the support of the medical profession as these methods of administration are not necessary and are not devoid of serious danger if adopted as routine methods in general practice

When administered by the mouth quinine may be given in the form of tablets capsules powders or in solution If possible solutions should be used as absorption is better and there is less irritation to the gastric mucosa than when powders or capsules are administered The sulfate of quinine should be dissolved by adding one drop (minim) of dilute hydrochloric or dilute sulphuric acid for 0 065 gm (one grain) of the drug being careful not to use an excess of the acid which would result in irritation of the stomach The bitter taste

It is especially deadly to the merozoites produced by segmentation, hence the well known favorable effect of a single large dose administered at the time of segmentation Upon the gametocytes quinine is most effective during their early stage of development but the administration of very large doses may be capable of destroying a certain proportion of fully developed gametocytes

The question as to whether the administration of quinine over long periods of time in doses insufficient to kill all plasmodia will result in the development of the so called quinine fast strains still is undecided Reasoning from analogy it is probable that such strains of the plasmodia might be developed in this manner, but there is no experimental evidence sufficient to prove that such strains actually exist in nature although it is true that in some regions infections with the same species of plasmodia are much more resistant to quinine than in others

As to choice of preparation it may be stated that there are three salts that are of real use the sulfate, the dihydrochloride and the tannate The sulfate is the most useful of these preparations and owing to its comparative cheapness the salt that should be used in treatment of mild infections and in prophylaxis The dihydrochloride (bihydrochloride of British Pharmacopeia) owing to its solubility should be used for subcutaneous, intramuscular and intravenous administration while the tannate owing to its less bitter taste, is especially suitable for administration to children The Italian authorities regard the latter salt as the ideal one for use in prophylaxis, owing to its slow rate of absorption and its more complete oxidation in the body

The time of administration of quinine in malarial infections varies with different observers but the writer believes that the best results are obtained by the administration of the drug at regular intervals throughout the twenty four hours in acute infections Where the malarial paroxysms occur regularly as in uncomplicated vivax and malariae infections the exhibition of a single large dose of quinine just before the time of segmentation is very effective in causing the disappearance of clinical symptoms, but the writer believes that better results are obtained even in these infections by divided doses of the drug administered at regular intervals The best results are secured in treating acute malarial infections by the administration of quinine every three or four hours in the proper doses as long as clinical symptoms of the infection persist

The dosage of quinine required in the treatment of malarial infections depends largely upon the type of the infections For instance smaller doses are required in treating most vivax and malariae infections than in the treatment of the falciparum infections Again the character of the symptoms present in any infection will influence the dosage of the drug as larger doses are required to conquer pernicious infections than benign infections while initial attacks are more amenable to quinine therapy than relapses It will thus be seen that it is

practically impossible to lay down any hard and fast rule regarding the dosage of quinine in malaria and the author believes that it is preferable to judge each case on its own merits and administer the drug in accordance with the severity of the symptoms which may be present

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can be somewhat disguised by employing some aromatic syrup or flavoring, but in most instances the patient soon becomes accustomed to it If the solution cannot be used the drug should be administered in capsules or powders, for while tablets may now be obtained that are easily soluble, it is wise to avoid them if possible

The rectal administration of quinine is seldom indicated and is the most inefficient of all the methods of administration In isolated instances, as profound anemia or cachexia where the pulse is very weak and the veins are so small as to make intravenous administration practically impossible, this method of administration may be tried from 8 to 10 ounces of saline solution (250 to 300 c c) containing from 1 3 to 2 gm (20 to 30 grains) of quinine being injected very slowly per rectum

The subcutaneous injection of quinine is in the writer's opinion, never justified as all that it can accomplish is more efficiently and safely accomplished by intramuscular injections It has been shown that no matter what precautions are taken there is always danger of abscess formation

The intramuscular injection of quinine received renewed impetus from the experiences of British surgeons in the treatment of malaria in Macedonia during World War I From their observations it is evident that this method of administration proved very useful and efficient in the treatment of the peculiarly severe falciparum infections prevalent among the troops in Macedonia the indications for this method of administration being a temperature over 104° F persistent vomiting mental symptoms as delirium, drowsiness, or stupor severe exhaustion cachexia and where the drug was not well absorbed by the stomach as shown by a thickly coated tongue

In administering quinine in this manner the following procedure should be followed The quinine solution should be made by adding 0 065 gm (one grain) of the dihydrochloride of quinine (bihydrochloride of British Pharmacopeia) to 0 065 c c (one minim) of distilled water i e one part of the drug to one part of distilled water and the usual dose for an injection is 2 5 c c (40 minims) of a solution containing 1 3 gm (20 grains) of quinine dihydrochloride The solution should be prepared if possible from freshly distilled water sterilized just before use by boiling If distilled water is not obtainable, boiled water may be used

The site selected for intramuscular injection is usually in the gluteal muscles, about two inches below the middle of the crest of the ilium The greatest care should be taken that strict asepsis is obtained The solution should be boiled before use as well as the syringe with which it is to be injected The skin over the site of injection should be scrubbed with hot water and soap and painted with tincture of iodin The needle should be introduced deep into the muscle care being taken that the solution does not get into the subcutaneous tissues and the injection should be made slowly and steadily After the withdrawal

of the needle the site of puncture should be painted with iodin and covered with sterilized gauze for a period of a few hours

Pain may be quite severe after an intramuscular injection and if the fluid has been injected into the subcutaneous tissues there is danger of abscess formation The injections should be repeated in from three to six hours and as often as the clinical symptoms indicate and in very severe infections or where pernicious symptoms are present an intravenous injection should be combined with the intramuscular

In making repeated intramuscular injections care should be taken to select sites removed at least an inch from preceding sites and where it is necessary to make numerous injections, the deltoid muscle may be used in addition for the purpose

The intravenous injection of quinine i the method par excellence where the most rapid action of the drug is desired as in pernicious attacks of malaria The indications for the administration of quinine in this manner are the occurrence of symptoms pointing to involvement of the central nervous system as marked delirium drowsiness stupor aphasia twitching of the muscles coma marked anemia or cachexia, very high temperatures algid choleraic or bilious types of infection and cases with marked jaundice

Baccelli was the first to advocate the intravenous administration of quinine in pernicious malarial infections and the solution that he employed contained 1 gm (15 grains) of quinine dihydrochloride to 10 c c (2 drams) of normal salt solution Although Baccelli s solution was used for many years for intravenous injection a number of fatalities due to its concentration were reported and to-day the quinine is used in much greater dilution The following method of preparing the solution of quinine for intravenous injection is recommended To 300 c c (ten ounces) of normal saline solution add 3 c c (50 minims) of quinine dihydrochloride solution containing 1 65 gm (25 grains) of the drug and sterilize by boiling Before using this solution it should be filtered carefully through sterilized gauze and heated to about 120° F before being placed in the reservoir for injection into the vein

In administering the solution of quinine the same precautions should be taken to avoid infection as in intramuscular injections of the drug The quinine solution should be placed in a properly graduated glass receptacle such as is used for injections of arsphenamine open at the top connected with a rubber tube in which there is a glass window and to which is attached a stopcock and a suitable needle for intravenous injection The entire apparatus should have been sterilized before the quinine solution is placed within it and the greatest care should be taken to see that the tubing and needle are kept free from contact with anything that is not sterile The skin over a large vein in the forearm is selected as the site for injection washed with hot water and painted with tinc

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The rectal administration of quinine is seldom indicated and is the most inefficient of all the methods of administration In isolated instances, as profound anemia or cachexia, where the pulse is very weak and the veins are so small as to make intravenous administration practically impossible this method of administration may be tried from 8 to 10 ounces of saline solution (250 to 300 c c) containing from 1 3 to 2 gm (20 to 30 grains) of quinine being injected very slowly per rectum

The subcutaneous injection of quinine is, in the writer s opinion never justified as all that it can accomplish is more efficiently and safely accomplished by intramuscular injections It has been shown that no matter what precautions are taken there is always danger of abscess formation

The intramuscular injection of quinine received renewed impetus from the experiences of British surgeons in the treatment of malaria in Macedonia during World War I From their observations it is evident that this method of administration proved very useful and efficient in the treatment of the peculiarly severe falciparum infections prevalent among the troops in Macedonia the indications for this method of administration being a temperature over 104 F persistent vomiting mental symptoms, as delirium, drowsiness, or stupor severe exhaustion cachexia and where the drug was not well absorbed by the stomach as shown by a thickly coated tongue

In administering quinine in this manner the following procedure should be followed The quinine solution should be made by adding 0 065 gm (one grain) of the dihydrochloride of quinine (bihydrochloride of British Pharmacopeia) to 0 065 c c (one minim) of distilled water i e , one part of the drug to one part of distilled water and the usual dose for an injection is 2 5 c c (40 minims) of a solution containing 1 3 gm (20 grains) of quinine dihydrochloride The solution should be prepared if possible from freshly distilled water, sterilized just before use by boiling If distilled water is not obtainable, boiled water may be used

The site selected for intramuscular injection is usually in the gluteal muscles about two inches below the middle of the crest of the ilium The greatest care should be taken that strict asepsis is obtained The solution should be boiled before use as well as the syringe with which it is to be injected The skin over the site of injection should be scrubbed with hot water and soap and painted with tincture of iodin The needle should be introduced deep into the muscle, care being taken that the solution does not get into the subcutaneous tissues and the injection should be made slowly and steadily After the withdrawal

of the needle the site of puncture should be painted with iodin and covered with sterilized gauze for a period of a few hours

Pain may be quite severe after an intramuscular injection, and if the fluid has been injected into the subcutaneous tissues there is danger of abscess formation The injections should be repeated in from three to six hours and as often as the clinical symptoms indicate, and in very severe infections, or where pernicious symptoms are present an intravenous injection should be combined with the intramuscular

In making repeated intramuscular injections care should be taken to select sites removed at least an inch from preceding sites and where it is necessary to make numerous injections, the deltoid muscle may be used in addition for the purpose

The intravenous injection of quinine is the method par excellence where the most rapid action of the drug is desired as in pernicious attacks of malaria The indications for the administration of quinine in this manner are the occurrence of symptoms pointing to involvement of the central nervous system as marked delirium drowsiness stupor aphasia twitching of the muscles coma marked anemia or cachexia, very high temperatures algid choleraic or bilious types of infection and cases with marked jaundice

Baccelli was the first to advocate the intravenous administration of quinine in pernicious malarial infections and the solution that he employed contained 1 gm (15 grains) of quinine dihydrochloride to 10 c c (2 drams) of normal salt solution Although Baccelli s solution was used for many years for intravenous injection a number of fatalities due to its concentration were reported and to day the quinine is used in much greater dilution The following method of preparing the solution of quinine for intravenous injection is recommended To 300 c c (ten ounces) of normal saline solution add 3 c c (50 minims) of quinine dihydrochloride solution containing 1 65 gm (25 grains) of the drug and sterilize by boiling Before using this solution it should be filtered carefully through sterilized gauze and heated to about 120 F before being placed in the reservoir for injection into the vein

In administering the solution of quinine the same precautions should be taken to avoid infection as in intramuscular injections of the drug The quinine solution should be placed in a properly graduated glass receptacle such as is used for injections of arsphenamine open at the top connected with a rubber tube in which there is a glass window and to which is attached a stopcock and a suitable needle for intravenous injection The entire apparatus should have been sterilized before the quinine solution is placed within it and the greatest care should be taken to see that the tubing and needle are kept free from contact with anything that is not sterile The skin over a large vein in the forearm is selected as the site for injection washed with hot water and painted with tinc

ture of iodine. The receptacle containing the solution is elevated, and a little of the solution allowed to flow through the tube thus getting rid of air bubbles and filling the injecting needle. The needle is then introduced through the skin over the vein and directly into the vein, keeping it as nearly parallel to the surface of the forearm as possible. The fluid is allowed to flow into the vein very slowly, governing the flow with pressure upon the rubber tubing or by means of the stopcock. When 240 c c (eight ounces) of the solution have flowed into the vein the needle should be withdrawn, the site of puncture painted with tincture of iodine and a small pad of sterile gauze applied. The 240 c c (eight ounces) of solution injected contains 1 3 gm (20 grains) of quinin dihydrochloride, and this is the usual dose for intravenous injection, but twice this amount of the drug can be administered without danger in the same amount of saline solution. While the dilution of quinine recommended is not as great as recommended by many authorities, the recent experience of the British in Macedonia has proved that it is sufficient in practice, and that no bad results have followed the administration of quinine in this concentration.

The intravenous injection of quinine should be repeated, if the clinical symptoms are not markedly affected within a few hours, and the same amount of the drug should be administered. Some authorities recommend as high as three injections of 1 3 gm (20 grains) each per day in very severe infections, but the writer believes that one intravenous injection of 1 3 gm (20 grains) combined with one or more intramuscular injections of the same amount of quinine dihydrochloride will be followed by better results and with less danger to the patient.

Contraindications to Quinine

There are some individuals, few in number, who have an idiosyncrasy for quinine and in whom the drug produces dangerous, or even fatal, symptoms.

The writer is convinced that most people, who state that they cannot take quinine, are self deceived, for in a very large experience he has only observed a very few instances where the drug could not be administered. To be sure, the symptoms following the exhibition of quinine in many instances have been disagreeable and hard to bear, but so far as danger to life is concerned or to the health of the individual his experience has been that in very few instances are we justified in withholding quinine in the treatment of malaria because of the statements of the patient that he cannot take the drug because of the symptoms produced by its administration. However, if hematuria, syncope, dyspnea, amaurosis or hemoglobinuria have followed the use of quinine, it is well to employ some substitute, but even in these cases it is questionable whether quinine should be abandoned if pernicious symptoms of malaria are present. Pregnancy is not a contraindication, for if the drug is administered carefully, the danger

of its producing abortion is much less than that attending the malarial infection if untreated If pernicious symptoms of malaria develop in a pregnant woman the infection should be treated as though pregnancy were not present for the life of the mother is endangered

Atabrine

Atabrine (quinacrine hydrochloride U S P mepacrine British name) is an alkyl amino-acridine derivative and was introduced for the treatment of malaria in 1933 At the present time (1945) it is the concensus of opinion of the medical staffs of our Army and Navy that it is superior to quinine in the treatment of acute attacks and in suppressive treatment as well as in the prevention of relapses thus confirming the statement of the writer made in 1938[47] that in atabrine we possess the best drug for the treatment of malarial infections Owing to the shortage of quinine during the late war it was necessary to employ atabrine almost exclusively in the treatment of malaria and the data accumulated from this experience has proven that it is practically curative after one course of treatment in falciparum malaria and will eliminate vivax and malariae infections if properly administered over a long enough period of time

Toxic symptoms rarely occur after the administration of atabrine and have already been discussed in the consideration of suppressive treatment with this drug The vast majority of individuals tolerate atabrine better than quinine and for this reason alone it is superior If toxic symptoms do develop quinine or totaquine should be substituted at once for atabrine

Atabrine kills the trophozoites schizonts and gametocytes of *Plasmodium vivax* and *Plasmodium malariae* and the trophozoites and schizonts of *Plasmodium falciparum* but its action if any upon the exo-erythrocytic forms of the plasmodia is unknown As in the case of quinine while atabrine will quickly control the acute symptoms of malaria it will not eliminate the infection unless it is administered over long periods of time

The dosage of atabrine employed in the treament of malaria varies with special conditions and will be discussed later

Totaquine

Totaquine is a combination of the alkaloids of cinchona and has been found to be effective in the treatment of malarial infections and may be employed in the absence of atabrine or quinine but not in preference to either of these remedial agents It is useless in the treatment of pernicious infections as it can be administered only by mouth

Plasmochin

Plasmochin a quinoline derivative, was introduced in the treatment of malaria in 1926 At the present time this drug is not employed in treatment except to destroy gametocytes if they be present and have not been eliminated by treatment with atabrine or quinine It is a very toxic drug when administered in larger doses than recommended for the purpose of eliminating gametocytes, and such doses are necessary to eliminate a malarial infection in susceptible individuals even the small doses recommended for gametocyte destruction are sometimes toxic

Plasmochin kills the trophozoites and schizonts of the tertian and quartan plasmodia but has no effect upon those of estivo-autumnal or sub tertian malaria However *it kills the gametocytes of all of the species of malaria plasmodia in very small and non toxic doses* a most valuable property, as it makes this drug available in preventing the tran mission of the plasmodia to the mosquito and thus eventually prevents the transmission of malaria by the mosquito to man The drug should be employed only for this purpose in practice all patients treated with quinine who show gametocytes in their blood receiving it, while of those treated with atabrine only those suffering from estivo-autumnal malaria should be given plasmochin for the reason that atabrine kills the gametocytes of tertian and quartan malaria

The specific treatment to be adopted in the therapy of malaria will vary somewhat with the drug employed and the clinical types of the malarial infections treated

Treatment with Atabrine

As already stated the writer believes that where the treatment of malarial infections can be supervised by a physician atabrine is today the drug of choice except in pernicious cases The experience of our Army and Navy with this drug during World War II has demonstrated that it cannot eliminate any malarial infection after only one course of treatment except in the case of falciparum malaria and that in vivax malariae and ovale malaria it must be administered over a long period of time in order to achieve that result In the case of falciparum malaria it has been found that even the dosage employed in suppressive treatment will eliminate a large proportion of falciparum infections

The initial treatment of all types of acute malaria with the exception of pernicious malaria, should be the same and consists in the administration of atabrine 0 2 gm (gr 3) and sodium bicarbonate 1 gm (15 grains) by mouth with 200 to 300 c c of water sweet tea or fruit juice every 6 hours for 5 doses followed by atabrine 0 1 gm (gr 1½) 3 times a day after meals for 6 days the

total amount of atabrine administered for the 7 days being 2 8 grams In uncomplicated cases of malaria the above dosage will cause the disappearance of all clinical symptoms but will not eliminate the infection In order to prevent relapses and eventually eliminate the infection this treatment should be followed after a lapse of one week or more by the administration of 0 1 gm (gr 1½) of atabrine 3 times a day for 3 days and followed by a daily dose of 0 1 gm for a period of 3 months Care should be taken that atabrine is not administered even in the smallest doses to individuals that have been found to be allergic to this drug

In patients who cannot retain the drug by mouth or in those in whom pernicious symptoms of malaria occur atabrine should be administered intramuscularly if it be employed at all in this class of infections The writer would always prefer to treat such infections intravenously with quinine but where quinine cannot be obtained atabrine should be given intramuscularly by injecting 0 2 gm (gr 3) in 5 c c sterile distilled water into each buttock total 0.4 gm (gr 6) using the usual precautions and avoiding massage Given in this manner it has been found that an effective plasma concentration is obtained in 15 minutes and maintained for 6 hours If necessary the intramuscular injections may be repeated once or twice at 6 hour intervals and as soon as the patient can retain anything by mouth atabrine should be administered orally until the total dosage by both routes equals 1 3 gm in 48 hours after which the usual treatment outlined above is instituted

The writer does not recommend the intravenous administration of atabrine and in all cases in which pernicious symptoms develop during an attack of malaria intravenous quinine should be given

Treatment with Quinine

If atabrine is not available or the patient cannot take this drug quinine should be employed in the treatment of malarial infections It is also true that where treatment cannot be supervised by a physician quinine should be the drug of choice or where it is necessary to administer a drug to large numbers of individuals in order to eliminate malaria i e to prevent relapses and medical supervision is impossible quinine is probably a safer drug to use than is atabrine

Treatment of Acute Attacks with Quinine — It has been ascertained by experience in treating many thousands of cases of malaria with quinine that while it is possible to control the symptoms of the acute attack in a few days with this drug it is necessary to continue its administration for several months in order to eliminate the infections The writer has found the following method of treatment satisfactory in cases of malaria which do not present pernicious symptoms

While symptoms are present 2 gm (gr 30) of quinine sulfate should be administered by mouth in divided doses, at intervals of 3 or 4 hours, and at least 0 65 gm (gr 10) of the drug should be administered thereafter for at least 3 months, either in a single dose at night or in equally divided doses morning and evening

If gametocytes are present plasmochin should be administered as described on a previous page If the blood is negative for gametocytes plasmochin should not be administered Usually the treatment outlined above, if the blood is free from gametocytes at the time of the onset of the acute symptoms, will prevent their development but it should be remembered that malaria may exist in a latent condition in man for various periods of time before acute symptoms develop and during this time gametocytes may have developed, and the patient may show them in the blood at the time of the acute attack As quinine has no effect upon the gametocytes it is evident that in such cases it should be followed by plasmochin which will destroy this phase of plasmodial development

The treatment of relapses in malaria is the same as for the acute attack, but in such cases quinine sulfate should be administered in larger doses after the disappearance of symptoms and over the same period of time At least 1 gm (gr 15) of quinine sulfate should be given daily for a period of 3 months after the acute symptoms have disappeared and in those patients showing gametocytes in their blood plasmochin should be administered as already recommended

Treatment of "Carriers" of Malaria with Quinine

A "carrier" of malaria may be defined as one presenting in his peripheral blood gametocytes of any of the species of malaria plasmodia, thus rendering him infective to the mosquitoes transmitting malaria Practically all individuals infected with malaria become carriers unless they have been properly treated and many carriers have not suffered from acute symptomatic attacks of their infection Carriers can only be diagnosed by a blood examination and every malarial patient should be examined most carefully and if gametocytes are present properly treated Such treatment is of vital importance in the prevention of malarial infections for if the gametocytes are destroyed, it is evident that mosquitoes cannot become infected and thus malaria cannot be transmitted

Quinine is of no practical value in ridding patients of gametocytes, and all such patients should be given a course of plasmochin as already recommended If blood examinations were made of all malarial patients and proper treatment were given all showing gametocytes in their peripheral blood, there is no question that the amount of malaria in regions where this is done, would be greatly reduced, and it is certainly a reproach to the medical practitioners in any malarial region, where these infections occur in great numbers, if they have been given

an opportunity to treat the infected individuals provided blood examinations have not been made and the carriers of malaria discovered and treated (See on a *following page Treatment with Plasmochin*)

Treatment of Pernicious Malaria

All patients suffering from an acute attack of malaria who develop pernicious symptoms should be given intravenous quinine at once unless there is an idiosyncrasy to the drug when atabrine should be given intramuscularly The technique and dosage of quinine for intravenous injection have already been discussed and will not be repeated here Prompt recognition of pernicious symptoms and prompt intravenous therapy will save many lives that would be sacrificed *otherwise and in all infections caused by Plasmodium falciparum a most careful* supervision of the patient is essential for the possible occurrence of pernicious symptoms

The Standard Treatment of Malaria

In 1918 the National Malaria Committee recommended for the routine treatment of malaria a course of quinine which had been recommended by a subcommittee after careful consideration This treatment known in the United States as the Standard Treatment has been employed very extensively in this country and when carefully followed has resulted in a great reduction of malaria in endemic localities and in the elimination of the infection in the majority of those who have adhered to the treatment as recommended Bass who has had a very large experience with this treatment states that the amount of quinine *recommended to be taken daily will cure from 60 to 70 per cent of* cases if taken for four weeks 80 per cent if taken for six weeks 90 to 95 per cent if taken for eight weeks and 100 per cent if taken for twelve to fifteen weeks

The Standard Treatment is as follows For the acute attack in adults 0 65 gm (ten grains) of quinine sulfate by mouth three times a day for a period of at least three or four days or until the acute symptoms disappear if they persist for over four days followed by the administration of 0 65 gm (ten grains) daily upon retiring for a period of eight weeks For infected individuals without symptoms the latter part only of the treatment is essential 0 65 gm (ten grains) daily

For children the doses of quinine recommended in this course of treatment are age less than one year 0 035 gm one year 0 065 gm two years 0 125 gm three and four years 0 2 gm five six and seven years 0 25 gm eight nine and ten years 0 35 gm eleven twelve thirteen and fourteen years 0 52 gm fifteen years and over 0 65 gm

Whenever the treatment of large numbers of infected individuals in malarial regions is to be attempted and it is desired to employ quinine the 'Standard Treatment will give excellent results if conscientiously followed

The League of Nations Method of Treatment of Malaria

The Health Section of the League of Nations has recommended that in the treatment of malaria quinine be administered only long enough to cause the disappearance of the symptoms of the acute attack after which the drug i stopped and relapses allowed to occur This method is based upon the fact that repeated attacks confer immunity to the particular strain of the malaria plasmodium causing the infection and that with the patient's acute symptoms being controlled by the quinine and relapses allowed to occur, an immunity should be required eventually While theoretically sound, this method of treatment is largely impractical exposes the infected individual to much discomfort and danger and for these reasons is not recommended It also favors the development of gametocytes during the latent periods of the infection and thus favors the infection of the mosquito and the transmission of malaria

Treatment with Plasmochin

While as already stated plasmochin was introduced originally for the treatment of all malarial infections it was soon found to be too toxic, when used in sufficient dosage to be used for that purpose but its unique destructive effect upon the gametocytes of all of the malaria plasmodia when employed in much smaller doses than were determined to be toxic renders it a most valuable specific in the treatment of carriers, i e those individuals presenting gametocytes in their blood

Plasmochin should never be employed in the routine treatment of malaria but should be given to all individuals whose blood shows the presence of gametocytes The original plasmochin was the hydrochloride but at the present time plasmochin naphtholate is used For the elimination of gametocytes plasmochin hydrochloride was administered in 0 01 gm (gr $\frac{1}{6}$) doses 3 times a day for 5 days but plasmochin naphtholate should be administered in twice this dosage or 0 02 gm (gr $\frac{1}{3}$) combined with 1 gm (gr 15) of sodium bicarbonate 3 times a day after meals for 4 days This treatment is usually successful in eliminating gametocytes and sterilizing the patient so far as the possibility of infecting mosquitoes is concerned

Plasmochin should never be administered to patients taking atabrine but may be given after the cessation of such treatment It may be administered during the latter portion of a course of treatment of acute symptoms with quinine while the latter drug is still being administered

Following plasmochin treatment the patient should have a liberal sugar and fluid intake and if toxic symptoms should occur the drug should be discontinued immediately In the experience of the writer toxic symptoms have never occurred after the dosage of plasmochin just recommended

Treatment with Totaquine

When neither atabrine or quinine can be obtained the mixture of the alkaloids of cinchona bark known as totaquine may be used with good results in the treatment of acute malarial attacks It should not be depended upon for the treatment of pernicious malaria or even severe attacks of malaria due to any of the malaria plasmodia and it must be administered by mouth Gastrointestinal symptoms frequently follow the exhibition of this combination and it should not be used if atabrine or quinine are available The dosage of totaquine is 1 gm (gr 15) 3 times a day after meals for 2 days followed by 0 65 gm (gr 10) 3 times a day after meals for 5 days

General Treatment

Aside from the specific treatment with quinine malarial infections should be treated symptomatically and if this is done in a careful and scientific manner the action of the specific drug is enhanced and the patient s recovery greatly hastened Symptomatic treatment during the acute attack of malaria is of great importance not only to the comfort of the patient but in saving life and the physician should not rest content with the administration of the specific drug but should study carefully the symptoms present and when necessary apply the proper therapeutic measures to conserve the strength of the patient and increase the effect of the specific drug

A cathartic is always indicated at the beginning of the treatment of the acute malarial attack and for this purpose the writer has found that minute doses of calomel followed by a saline purge give the best result The use of a cathartic appears to increase the effect of quinine probably by favoring absorption The administration of a carminative is recommended by some authorities who state that carminatives favor the absorption of quinine and thus help in quickly overcoming the infection

During the chill the external application of heat in some form is very grateful and in algid pernicious malaria hot water bottles and electric pads should be used to conserve the body heat During the warm stage sponging with tepid water may be employed and if the fever is excessive cold baths should be given Antipyretics should be avoided as most of them are heart depressants and the fever can be better controlled by hydrotherapeutic measures If marked nervous

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ness severe headache or delirium be present morphine may be given, but the writer has very seldom found this to be necessary and the drug should be used with the greatest caution in these cases

During the decline in the fever, symptoms of collapse may develop, and these should be treated by external application of heat the use of intravenous normal saline solutions and hypodermics of atropine and brandy In cases presenting severe vomiting mustard plasters may be applied over the epigastric region and small doses of morphine may be administered The sucking of cracked ice or sipping of iced champagne sometimes relieves this distressing symptom In pernicious cases presenting choleraic or dysenteric symptoms the diarrhea should be checked with the usual remedies, of which opium is among the best, and if the patient is much exhausted and weakened, the intravenous injection of normal saline solution should be practiced

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CHAPTER XXXII-A

PAPPATACI FEVER

By COL. CHARLES CRAIG, Medical Corps, U. S. Army (Retired), D.S.M.

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Synonyms.—Sand fly fever, phlebotomus fever, three day fever, summer fever, Mediterranean dengue.

Definition.—An acute specific fever of sudden onset, characterized by muscular aching, nervous symptoms and gastrointestinal disturbance, the febrile paroxysm usually lasting for three days and terminating by crisis. It is caused by a filterable virus transmitted from man to man by the sand fly, *Phlebotomus papatasii*.

History

Pym in 1804 first described this fever as occurring in the Mediterranean region and English army surgeons repeatedly noted its occurrence in Malta, hence the name "Mediterranean dengue," owing to the resemblance of the symptomatology to that of dengue fever. In 1887 Pick gave an excellent description of the disease and in 1903 McCarrison described it as occurring in India, calling it the "three day fever of Chitral," and first called attention to the possible connection of sand flies with its transmission. In 1905 Taussig described cases occurring along the Adriatic coast, and in 1907 Doerr, Franz and Taussig, after a careful experimental study of the fever, demonstrated that it is due to a filterable

is transmitted through the eggs and larvae of the sand fly to the adult but this hereditary transmission in the flies has not been confirmed by other investigators

Birt in 1908 using sand flies allowed to bite individuals suffering from the fever during the first twenty four hours after onset and then taken to Netley England where the disease does not occur and allowed to bite healthy individuals successfully produced the fever in volunteers thus confirming the observations of Doerr Franz and Taussig

Whittingham believes that the virus may pass the winter in the soil or in the larvae of *P papatasii* infected through feeding on the feces of the adult flies but these observations have not been confirmed In 1922 Whittingham obtained a spirochete resembling *Leptospira icterohemorrhagiae* from the blood during the first twenty four hours after onset of the fever but was unable to produce the fever in human volunteers with the cultures and a similar spirochete obtained by Couvy in cases diagnosed as dengue but with identical symptoms also failed to produce the disease It is probable that both observers were dealing with some other disease than either pappataci fever or dengue The period of infectivity in the fly is not known

The intravenous injection of blood into monkeys produces a febrile reaction Shortt Rao and Swaminath (1936) were first successful in cultivating the virus of this disease upon the chorio-allantoic membrane of embryo chicks and their work has been confirmed by Shortt Pandit and Rao (1938–39) They have demonstrated that the blood sera of convalescents from the fever neutralizes the virus cultivated in the chick as it was impossible to produce the disease in human volunteers after treatment of the virus with convalescent serum In 1941 Anderson was able to diagnose pappataci fever by cultivating the virus in chick embryos from the blood of suspected cases but obtained positive results in only 78 of 132 cases

EPIDEMIOLOGY

Pappataci fever occurs in widespread epidemics and is apparently almost confined to sub-tropical and tropical countries although cases have been observed in the Himalayas at an altitude of over 7000 feet Usually it is limited to low lying moist regions hence it is especially prevalent along the coastal regions of the countries in which it has been studied In temperate regions it occurs during the summer months at which time the sand flies are most numerous and while it occurs in epidemic form during which almost the entire population may be affected it also occurs endemically and non immune individuals may become infected at any time so long as sand flies are prevalent As the adult sand flies do not live through the winter in temperate climates the persistence of this disease from season to season is not understood unless the

virus present in the blood during the first twenty four hours of the disease and transmitted by the sand fly, *Phlebotomus papatasii* In 1936, Shortt, Rao and Swaminath were successful in cultivating the virus of sand fly fever upon the chorio allantoic membrane of embryo chicks

Geographical Distribution

Owing to its marked resemblance in symptomatology to mild cases of dengue fever it is probable that the exact geographical distribution of this fever is still undetermined as both dengue and pappataci fever often occur in the same localities and it is often impossible to differentiate them However the fever seems to be limited to the sub tropics and tropics and has been observed in all of the countries bordering upon the Mediterranean, in Italy Corsica Sicily Malta Cyprus and Crete Portugal the south of France, Spain, Algiers and Tunis Cases of infection have been observed in Central France and in the Balkans It occurs in Egypt Syria Palestine Turkey, Mesopotamia, the Sudan and Uganda, and in India it occurs in Peshawar, Chitral, Ceylon, the Straits Settlements and China In the Western Hemisphere it has been noted in Brazil Guatemala Ecuador Central America and the coast region of Mexico Cases have been described in the southern portion of the United States but are questionable It is probable that pappataci fever has a much wider distribution than is now known and that it occurs wherever the transmitting insect *Phlebotomus papatasii*, is found

Etiology

The cause of pappataci fever is known to be a virus that is filterable but aside from this its nature is unknown In 1907, Doerr Franz and Taussig allowed sand flies (*P papatasii*) to bite patients suffering from this disease and afterwards to bite healthy individuals in Vienna, where the fever never occurs Some of the healthy individuals bitten by such flies developed the fever but only when the flies had bitten the patient during the first twenty four hours after the onset of the fever and after a period of one week had elapsed before the infected flies bit healthy individuals These investigators proved that the virus passes through Berkefeld Reichelt and Pasteur Chamberland (candle F) filters but not through the Puckall filter that the virus is in the circulating blood only during the first twenty four hours of the fever, as blood taken after that period and injected intravenously into human volunteers invariably failed to produce infection while blood taken during the first twenty four hours injected intravenously produced the typical disease and that the virus remains infective for several days in blood kept at low temperatures Doerr claims that the virus

is transmitted through the eggs and larvae of the sand fly to the adult but this hereditary transmission in the flies has not been confirmed by other investigators

Birt in 1908 using sand flies allowed to bite individuals suffering from the fever during the first twenty four hours after onset and then taken to Netley England where the disease does not occur and allowed to bite healthy individuals successfully produced the fever in volunteers thus confirming the observations of Doerr Franz and Taussig

Whittingham believes that the virus may pass the winter in the soil or in the larvae of *P papatasii* infected through feeding on the feces of the adult flies but these observations have not been confirmed In 1922 Whittingham obtained a spirochete resembling *Leptospira icterohemorrhagiae* from the blood during the first twenty four hours after onset of the fever but was unable to produce the fever in human volunteers with the cultures and a similar spirochete obtained by Couvy in cases diagnosed as dengue but with identical symptoms also failed to produce the disease It is probable that both observers were dealing with some other disease than either pappataci fever or dengue The period of infectivity in the fly is not known

The intravenous injection of blood into monkeys produces a febrile reaction Shortt Rao and Swaminath (1936) were first successful in cultivating the virus of this disease upon the chorio-allantoic membrane of embryo chicks and their work has been confirmed by Shortt Pandit and Rao (1938–39) They have demonstrated that the blood sera of convalescents from the fever neutralizes the virus cultivated in the chick as it was impossible to produce the disease in human volunteers after treatment of the virus with convalescent serum In 1941 Anderson was able to diagnose pappataci fever by cultivating the virus in chick embryos from the blood of suspected cases but obtained positive results in only [illegible]8 of 132 cases

EPIDEMIOLOGY

Pappataci fever occurs in widespread epidemics and is apparently almost confined to sub-tropical and tropical countries although cases have been observed in the Himalayas at an altitude of over [illegible],000 feet Usually it is limited to low lying moist regions hence it is especially prevalent along the coastal regions of the countries in which it has been studied In temperate regions it occurs during the summer months at which time the sand flies are most numerous and while it occurs in epidemic form during which almost the entire population may be affected it also occurs endemically and non immune individuals may become infected at any time so long as sand flies are prevalent As the adult sand flies do not live through the winter in temperate climates the persistence of this disease from season to season is not understood unless the

virus is transmitted hereditarily through the eggs and larvae to the adult flies, as claimed by Doerr One attack of the disease confers a rather lasting immunity but second and third attacks have been recorded although somewhat rare Natives in the endemic areas possess an immunity to the disease Doerr demonstrated that the blood serum from convalescents rendered harmless infective serum when mixed with it and that this power was retained by convalescents as long as two years after recovery from the disease For the occurrence of epidemics it is necessary that a large non immune population be available and this explains the frequent occurrence of such epidemics in armies operating in the endemic areas or in bodies of troops stationed in such areas and coming from localities where the disease does not occur

The sand fly may bite by day as well as by night and has a very limited range of flight Hence pappataci fever occurs often in limited areas, or even in certain houses and it has long been known that individuals living in the upper stories of buildings do not suffer from the disease to the same extent as those living on the first or second floors Temperatures below 70 F (21° C) are fatal to the sand fly and this explains the occurrence of the disease in the hot summer months and its disappearance with the coming of the autumn and winter

Epidemics of pappataci fever vary considerably in severity and this may be explained by conditions favorable or unfavorable to the propagation of sand flies While *Phlebotomus papatasii* is the most common transmitter of this fever two other species have been incriminated i e *P minutus* and *P perniciosus* These flies breed in damp dark places and the complete development from egg to adult insect varies from one to two months according to the temperature The eggs are deposited most frequently in cracks in old damp walls in caves and in damp ground surrounding dwelling places Their small size enables them to pass through ordinary screens and mosquito nets Too much moisture kills them so that the advent of the rainy season in places where they occur quickly stops epidemics of pappataci fever The life of the insect is short under natural conditions and in the laboratory they seldom live for more than 2 to 3 weeks

Pathology

Morbid Anatomy —Death from pappataci fever is practically unknown, and nothing is known of the lesions if any produced by the infection There have been a few post mortems made upon individuals dying during an attack of this fever but in all such cases the only lesions observed were those of the complication which caused the death of the patient

The Blood —The most important changes are observed in the blood, a marked leucopenia being present in most cases the leucocytes numbering from 2 500 to 4 000 with a decrease in the polymorphonuclears and an increase in the

large mononuclear leucocytes The eosinophiles are reduced in number during the febrile period but return to normal or are increased during convalescence

The Urine — The urine is reduced in amount and the specific gravity is increased Albumin is almost invariably absent but rare instances are recorded of a slight trace of albumin being noted in the urine during the second or third day of the fever Ehrlich s diazo reaction is negative and the reaction of the urine is acid The virus is not present in the urine

Symptomatology

Incubation Period — In the experimental cases of Doerr Franz and Taussig the incubation period varied between three days and sixteen hours to seven days while under natural conditions the period varies from three to nine days the usual period being from three to six days

Symptoms — Prodromal symptoms rarely occur consisting of malaise slight muscular pains loss of appetite and a sense of tiredness Usually the attack is sudden in onset with very slight chilly sensations and a rapid rise of fever to 102° to 103 F or higher (38 9 –39 4° C) the fever reaching its height within twenty four hours Temperatures greater than 104° F (40 C) are very seldom observed With the rise in temperature the patient develops severe headache post-orbital pain and tenderness on pressure over the eyes a flushing of the skin sometimes resembling an erythematous eruption severe muscular pains which are general but especially severe in the lumbar region tenderness of the muscles upon pressure injected conjunctivae and great nervous irritability Vomiting may be present at the onset and there may be severe epigastric pain The bowels usually are constipated but diarrhea may be present The loss of appetite is extreme many patients refusing food or becoming nauseated at the sight or thought of it The tonsils and mucous membrane of the mouth and pharynx are congested the tongue covered with a yellowish white fur with clean tip and sides There may be slight nasal catarrh or a slight bronchitis Insomnia may occur but usually the patient has periods of drowsiness The sense of taste frequently is abolished during the febrile paroxysm

Among other symptoms which have been noted may be mentioned conjunctival hemorrhages painful and swollen articulations epileptiform convulsions hemorrhage from the bowel epistaxis and pain in the bones

The fever reaches its maximum within twenty four to thirty hours remains practically stationary for a day and then falls by crisis the entire febrile paroxysm lasting three days In some cases the temperature falls to normal at the end of the first day while in others it may extend through the fourth day It is noted by all observers that afebrile cases occur although it is probable that in these cases ephemeral fever of very short duration occurred at some time Cases

have been reported in which the fever lasted for seven to nine days but it is believed that all such patients were really suffering from dengue instead of pappataci fever

In this disease the lymph nodes are not enlarged, a valuable differential point in the diagnosis between it and dengue and the liver and spleen are not enlarged

Physical Signs — The *skin* is much flushed and often appears to be covered with an erythematous eruption It is usually dry, but sweating may occur especially at the time of decline of the temperature Subcuticular mottling of the skin of the chest and abdomen is often present, and rarely a minute papular eruption is said to occur Here again dengue may have been the condition observed rather than pappataci fever

The *pulse* is relatively slow as compared with the temperature in most cases and this bradycardia may continue throughout convalescence Otherwise the heart is normal and no murmurs can be detected

After the fever falls the symptoms disappear and convalescence begins The convalescence usually is slow, a remarkable amount of debility existing wher one considers the slight duration of the febrile paroxysm Relapses are very rare but do occur and in a few cases a continued irregular temperature has been observed lasting for several days Usually in from three to four weeks the patient has regained his normal health

Complications and Sequelae

Both complications and sequelae are very rare Among the complications may be mentioned epistaxis and hemorrhage from the bowel bronchitis bronchopneumonia parotitis orchitis chronic enteritis and nephritis There are no sequelae unless the debilitated condition following an attack is so considered

Diagnosis

The diagnosis of pappataci fever is by no means easy and its differential diagnosis from dengue frequently is impossible The occurrence of a fever ending in three days accompanied by sudden onset general muscular pain erythematous flushing of the face greatly injected conjunctivae leucopenia and bradycardia is exceedingly suggestive If this condition develops during the hot season when sand flies are numerous and in the person of one, who has recently come into the known endemic area of the disease the diagnosis of pappataci fever is justifiable It should be remembered that mild cases occur in which the symptoms are slight and the fever may last for only twenty four hours or less and in such cases the diagnosis is impossible

The diseases most apt to be confused with pappataci fever are malaria,

dengue influenza relapsing fevers paratyphoid and typhoid fevers in the initial stages and other fevers of short duration

Malaria may be differentiated by the finding of the plasmodia in the blood the presence of severe chills and the absence of leucopenia *Dengue* offers the greatest difficulty in differential diagnosis and it is certainly true that many cases of dengue cannot be differentiated from pappataci fever However the *shorter duration of the fever the absence of lymph node enlargement and of the* terminal eruption differentiates pappataci fever from dengue in average infections It is impossible to differentiate some mild cases of dengue from pappataci fever

Influenza is differentiated by the presence of more pronounced respiratory symptoms and the occurrence of this infection during cold weather If influenza occurs during the hot season as it sometimes does in the tropics and respiratory symptoms are not pronounced the differential diagnosis may be very difficult and sometimes impossible *Relapsing fevers* of short duration may simulate pappataci fever but the demonstration of the causative spirochete in the blood in relapsing fevers serves to differentiate them *Yellow fever* when mild might cause confusion but even moderately severe cases of yellow fever can be easily differentiated by the temperature curve the presence of albumin in the urine and the development of jaundice *Paratyphoid* and *typhoid fevers* could be confused only in the initial stages of their development and the continuation of the fever alone will suffice to distinguish these fevers *Typhus* and pappataci fever are difficult to distinguish at the time of onset but the presence of leucopenia in pappataci fever and the absence of the characteristic eruption of typhus should render a differential diagnosis possible

The *leucopenia in pappataci fever is important from a diagnostic standpoint* and pursues a fairly characteristic course On the first day of the disease there is a relative and absolute decrease in the lymphocytes accompanied by a relative and sometimes absolute increase in the neutrophiles During the second and third days of the disease the number of lymphocytes increases while the number of *segmenting neutrophiles drops and the immature cells increase so that they* may outnumber the segmenting cells By the 5th to 8th days after the disappearance of the fever the blood picture becomes normal Because of these changes in the leucocyte picture during the stages of the disease it is best to examine the blood every day if possible

Prognosis

The prognosis is always *excellent as death never occurs in uncomplicated* cases Complications are very rare but the debility following the infection may persist for several weeks

Prophylaxis

Prophylaxis consists in the prevention of the breeding of sand flies and protection from their bites The patients should be isolated and carefully screened in order to prevent the infection of the flies, and it should be remembered that the ordinary mosquito net is ineffective as sand flies can pass through the mesh A net containing at least 22 holes to the linear inch should be employed As sand flies do not fly higher than ten feet, sleeping in the upper stories of houses is a good prophylactic measure Repellents, as oil of citronella anise, eucalyptus or clove mixed with liquid petrolatum or lanolin and smeared upon the skin are very useful in preventing sand fly bites After dark the clothing should be of such character as to expose as little of the person as possible, and the use of electric fans in rooms is an efficient prophylactic measure as sand flies will not enter rooms in which a strong current of air is present

As the sand flies breed in collections of rubbish where there is shade and moisture such collections should be removed and other breeding places as latrines ruined walls in which the flies breed in the cracks and moist cracks in the ground should be removed or the cracks filled up with suitable material Latrines may be fumigated with sulphur or burned out with oil

With the advent of DDT as an insecticide it is now possible to control the spread of pappataci fever as has been proven in the case of our troops operating in endemic areas of the disease during World War II The methods of prophylaxis that have been found most efficient by our medical officers, have been the use of the DDT residual spray in treating walls where the insects breed, and in spraying the walls and ceiling of dwelling places and barracks combined with the use of repellents The repellent employed in our armies protected the individual from the bites of these flies for from 4 to 6 hours an application being made at sundown and a second upon retiring It has been found that the regular use of repellents has proven an effective method of preventing pappataci fever For methods of using DDT the reader is referred to the discussion of the subject in the section in this work upon Malaria (Chapter XXXII, Vol V)

Treatment

The treatment of pappataci fever is purely symptomatic The bowels should be opened with small doses of calomel followed by a saline, and the patient should be at rest in bed Food should not be urged upon the patient as it is better to withhold food than to force it when anorexia is present Pain may be controlled by acetylsalicylic acid (aspirin) in doses of 0 3 gm (5 grains) every four or five hours and rubbing with a good liniment is often grateful to the patient As the disease is of such short duration and excellent prognosis,

remedial measures beyond those which will keep the patient comfortable are not indicated Convalescence is slow and tonics and a nourishing diet are es sential

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CHAPTER XXXIII

AMEBIASIS

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noted later demonstrated beyond doubt the pathogenic nature of *Endamœba histolytica* and the non pathogenic nature of *Endamœba coli* through experimental infections in man

Since the discovery of the two amebae mentioned other species have been found to live in the human intestine Prowazek (1911-1912) described a species which is now known as *Iodamœba butschlii* while Wenyon and O Connor (1917) described another species now known as *Endolimax nana* A fifth species known as *Dientamœba fragilis* was described by Jepps and Dobell in 1918 All of the species are regarded as non pathogenic with the exception of *Endamœba histolytica*

The cultivation of *Endamœba histolytica* in vitro was first accomplished by Cutler (1918) but to Boeck and Drbohlav (1924-1925) belongs the credit of evolving the first media upon which this ameba can be cultivated for indefinite periods There are now many suitable media for the cultivation of this parasite but pure cultures have not yet been obtained

The serology of amebiasis has been investigated by several workers and the writer (1927) demonstrated the presence of hemolytic and cytolytic bodies in cultures of *Endamœba histolytica* and described (1929) the technique of a complement fixation test which has proven most useful in the diagnosis of amebiasis in man

The observations regarding complement fixation as a useful diagnostic method in amebiasis have been confirmed by Menendez (1932) Heathman (1932) Spector (1932) Tsuchiya (1932) Weiss and Arnold (1934) Meleney and Frye (1935-1937) Stone (1935) Paulson and Andrews (1936) Rees Bozievich Reardon and Jones (1942) and others and various useful modifications of his original test have been published within recent years

The modern conception of amebiasis was first stated clearly by the writer in 1921 for prior to that time amebic dysentery was regarded as a disease entity but at the present time all well informed physicians recognize that dysentery is simply a symptom of amebiasis and that while amebiasis often is manifested clinically by symptoms of diarrhea or dysentery it is responsible for many other clinical symptoms many of which have no connection with the intestinal tract beyond the fact that the original infection was derived from that tract The recognition of the true character of amebiasis has been a great step in advance in its history and has been followed by the institution of proper methods of prophylaxis and treatment

Geographical Distribution

The geographical distribution of amebiasis is world wide although infections are more often encountered in the tropics or sub-tropics than in temperate

Synonyms — Amebic dysentery entamebic dysentery, endamebic dysentery, amebic colitis amebic enteritis

Definition — The clinical term, "amebiasis", properly defined, means the invasion of any of the tissues of man by the pathogenic ameba, *Endamœba histolytica*, although it is usually limited by the clinician to invasion of the tissues of the intestine by this parasite It includes all degrees of pathology produced by this ameba from the minute microscopic lesions in symptomless carriers to the severe macroscopic ulcerations observed in individuals suffering from the symptom complex of amebiasis known as amebic dysentery, or the abscesses produced in various organs especially the liver It is most essential to recognize that the term 'amebiasis denotes any invasion of any of the tissues of man by *Endamaba histolytica* and that 'amebic dysentery" is simply a symptom complex which may or may not be met with in amebiasis

History

In 1875 Losch described an ameba occurring in the stools of a patient suffering from acute dysentery in St Petersburg, Russia, which he named "*Amœba coli* and which was identical with the ameba now known as *Endamœba histolytica* Although Losch found the ameba later at autopsy in the ulcerations which were present in the large intestine and produced dysentery in a dog by the rectal injection of fecal material from this patient, he did not consider the ameba as the cause of the dysentery and it was not until Kartulis (1886) published the results of his researches upon the etiology of acute dysentery in Egypt that this ameba was considered as the cause of dysentery in man The observations of Kartulis were followed in 1891 by those of Councilman and Lafleur, who concluded that amebic dysentery is a clinical entity characterized by definite pathologic lesions and caused by the ameba described by Losch, known as " *Amœba coli* The later publications of Quincke and Roos (1893), Roos (1894) and Huber (1903) all confirmed the work of the previous investigators but it had been noted by all investigators that amebae also occurred in the stools of normal individuals and those suffering from other diseases but especially by Quincke and Roose (1893) who described the morphological differences between the common ameba occurring in health and other diseases and the pathogenic ameba causing amebic dysentery However, it was not until the publication of his researches by Schaudinn (1903) that there was general acceptance of a pathogenic and a non pathogenic species of ameba living in the intestine of man Schaudinn called the pathogenic ameba *Entamœba histolytica* and the non pathogenic ameba *Entamœba coli* Further observations by the writer (1905) Werner (1908) and Hartmann (1909) confirmed Schaudinn s observations and the work of Walker and Sellards (1913) which will be

dysentery to the same extent that they did during the invasion of the Philippines during the first World War due to the preventive measures adopted by the Army Medical Corps and to improved methods of control and treatment

Etiology

The cause of amebiasis is an ameba *Endamaeba histolytica* an organism belonging to the protozoa class rhizopoda The intestine of man is parasitized by no less than five species of amebae all belonging to the Rhizopoda but only one of which is capable of producing lesions and disease These amebae are *Endamaeba histolytica* the pathogenic species *Endamaeba coli* *Endolimax nana* *Iodamaeba butschlii* and *Dientamaeba fragilis* none of which are pathogenic

The differentiation of these various amebae is made upon differences in nuclear structure the morphology of the cystic stage of development and differences in their life history The morphology of *Endamaeba histolytica* and its differential diagnosis from the other intestinal amebae of man will be considered in the section treating of Diagnosis in order to avoid needless repetition

The habitat of *Endamaeba histolytica* is in the lumen and tissues of the intestine of man and some of the lower animals most frequently in the large intestine although lesions due to its presence have been found in the lower portion of the ileum but in the writer s experience always accompanied by lesions in the large intestine This ameba may live in other parts of the body as in the liver spleen brain and other organs where it may produce abscesses and it has also been described as occurring in the bladder testis epididymus gall bladder the lymph nodes in Hodgkin s disease and in the bones In the tissues in man *Endamaeba histolytica* always occurs as the motile form or trophozoite in the writer s experience

The life cycle of *Endamaeba histolytica* is simple consisting of a vegetative a pre-cystic and a cystic stage of development In the vegetative stage of development the parasite always occurs as a motile organism the trophozoite while in the pre cystic and cystic stages of development motility is lost and the organism becomes spherical in shape The cysts are the infective stage of the parasite as the motile forms are killed while passing through the stomach by the hydrocholoric acid of the gastric juice which does not affect the cysts When the cysts of *Endamaeba histolytica* are swallowed by man in contaminated food or drink they pass unharmed through the stomach and in the lower portion of the ileum and the upper portion of the colon excystment occurs a four nucleated ameba emerging from the cyst which after a rather complicated series of nuclear divisions gives rise to eight motile trophozoites Excystment usually occurs in the upper portion of the colon in the ileo-cecal region but that it may occur in the lower porton of the ileum is evidenced by the occurrence of amebic ulceration in this region as already noted

regions, largely due to unsanitary conditions prevailing in many localities in the tropics and sub tropics The symptom-complex of amebiasis known as amebic dysentery is observed far more frequently in the tropics and warm countries than in cold regions hence the prevalent conception by the medical profession that amebiasis and amebic dysentery are tropical conditions, for until recent times it was not recognized that amebic dysentery is simply a part of the clinical picture of amebiasis It should be remembered that amebiasis occurs frequently even in temperate and cold regions, and that amebic dysentery, while far less often observed in such regions does occur and much more frequently than is usually believed

Recognizing that amebiasis is of world wide distribution, the distribution of the important symptom complex amebic dysentery, is of interest, for while amebic dysentery occurs wherever amebiasis does it is much more prevalent in certain regions than in others, and its distribution is, therefore, of medical importance

In North America amebic dysentery is seen most frequently in the Southern United States especially in Louisiana Texas Florida, Georgia, Mississippi and Alabama, but numerous cases occur in California, Virginia, the Carolinas, Tennessee and sporadic cases have been observed in practically every State of the Union as well as in Canada

In Central and South America amebic dysentery is prevalent in Mexico Guatemala Honduras Nicaragua Panama Colombia Chili Peru, Venezuela, Equador Brazil and the Argentine Republic but occurs sporadically throughout all of tropical and sub-tropical America and in the islands of the West Indies especially in Cuba, Haiti and San Domingo and Puerto Rico Wherever sanitation is poor in these countries amebic dysentery is common

In Europe amebic dysentery occurs sporadically in every country but is common in Russia Poland, Turkey, Greece Italy, Malta, Sardinia and Spain In Asia it is prevalent in Mesopotamia Palestine Syria, India, China, the East Indies Cochin China Siam the Malay States, Formosa, Korea and Japan In the Philippines amebic dysentery used to be one of the most prevalent and fatal infections but within recent years due to improved sanitary conditions, it is encountered much less frequently In Africa amebic dysentery occurs frequently throughout the tropical belt and sporadically throughout that continent It is most frequently encountered in Egypt Algeria, Tunis Tripoli, British East Africa the Congo basin Togo the Ivory Coast and the regions bordering upon the great lakes and rivers

In the South Pacific amebiasis and amebic dysentery are prevalent in the Solomon Islands New Guinea New Caledonia, New Hebrides, Fiji New Ireland, the Gilbert and Ellice Islands Bougainville and New Britain At the date of writing (1945) our troops serving in these islands have not suffered from amebic

Cysts are passed in the feces containing one, two, three or four nuclei and it has been usually believed that nuclear division does not occur in such cysts after passage from the intestine. Hegner, Johnson and Stabler (1932) and Tsuchiya (1932) have found that under favorable conditions of moisture and temperature the uni- and binucleate cysts will develop into the quadrinucleate cyst in fecal material after leaving the intestine.

The cultivation of *Endamœba histolytica* probably was first successfully accomplished by Cutler (1918) but to Boeck and Drbohlav (1924–1925) belongs the credit of first evolving culture media upon which this ameba can be cultivated indefinitely. Since their results were published numerous observers have described excellent culture media which will be considered later. At the present time it is possible to cultivate *Endamœba histolytica* upon numerous media for months and even years but always in association with the bacteria with which they occur in the intestine of man or animals, as pure cultures have not been obtained which could be transferred for more than a few days. The writer has maintained a strain of *Endamœba histolytica* in culture in vitro for over five years during which time no change occurred in the morphology of the organism and practically no loss in its virulence in kittens.

Experimental infection of some of the lower animals with *Endamœba histolytica* with the production of lesions more or less closely resembling those found in infection in man has been accomplished by numerous authorities either by feeding material containing the cysts of the parasite or by rectal inoculation of the motile trophozoites. The dog has been experimentally infected by Losch (1875), Hlava (1887), Harris (1901), Dale and Dobell (1917) and Faust (1930); the cat by many observers, notably by Marchoux (1899), Craig (1905), Wenyon (1912), Rees (1929), Martin (1930) and Frye and Meleney (1932–1933); the monkey by Musgrave (1906), Dobell (1931) and Hegner, Johnson and Stabler (1932); the guinea pig by Baetjer and Sellards (1914) and Chatton (1918); the rat by Lynch (1915), Brug (1919), Kessel (1928), Chiang (1925), Tanabe (1934) and others; the rabbit by Huber (1909) and Thomson (1926); and the domestic pig by Kessel (1928). Of all of these animals the dog presents experimentally lesions which are most like those which are seen in man, and in both the dog and the cat amebic abscess of the liver has occurred after experimental infection of the intestine. Both cultures of *Endamœba histolytica* and fecal material containing the parasite may be employed successfully in producing infection in the animals mentioned.

Naturally acquired infections with *Endamœba histolytica* have been observed in monkeys, rats and in the dog, and it is probable that other animals may harbor this ameba and may act as transmitting agents of the infection.

Relation to Disease.—At the present time there is no doubt that *Endamœba histolytica* is capable of producing a form of severe dysentery in man

After the division of the ameba liberated from the cyst, the motile trophozoites attack the mucous membrane of the intestine and by means of a cytolytic substance which they excrete and their ameboid motility dissolve and penetrate the tissues eventually producing the ulceration of the intestine so characteristic of amebic dysentery The trophozoites multiply in the tissues by simple division, the nucleus first dividing followed by the division of the ameba into two amebæ As long as conditions are favorable for the division of the trophozoites cysts are not formed but if conditions become unfavorable for this stage of existence the trophozoites round up become spherical in shape, secrete a cyst wall and nuclear multiplication occurs within the cyst until four nuclei are developed at which time the cyst is fully developed and is infective to man if swallowed in food or drink contaminated with the feces containing the cysts, when the life cycle described is repeated The pre cystic forms are the motionless rounded up trophozoites just prior to the development of a cyst wall and the multiplication of the nucleus within the cyst and resemble the trophozoites except that they are smaller and have lost their motility The motile trophozoites which do not penetrate into the tissues of the intestine, probably multiply as trophozoites in the lumen of the bowel for a limited period of time but eventually encyst

It is still unknown whether *Endamœba histolytica* can live and multiply as a trophozoite in the bowel lumen without invading the tissues but the fact that this ameba is essentially a tissue parasite and that even in carriers, who present no symptoms lesions have been found in the bowel is, in the opinion of the writer sufficient to negative the idea that *Endamœba histolytica* is ever exclusively a lumen dweller in the intestine of man It is believed that in every individual infected with this parasite there is constant invasion of the tissues of the intestine by it and that in every such individual microscopic, and very frequently macroscopic lesions are produced by such invasion even though clinical symptoms may be absent as they frequently are when natural resistance is good

The method of reproduction of *Endamœba histolytica* in the motile or trophozoite stage of existence is by simple binary fission first of the nucleus succeeded by the body of the ameba The division of the nucleus has been claimed to be mitotic in character by some authorities while others claim it is amitotic Probably it is by a modified form of mitosis according to the best evidence available

The method of reproduction within the cysts is by the division of the nucleus into two nuclei each of which later again divides into two, thus producing a four nucleated cyst As already noted excystment of this four nucleated ameba is followed by a division of the four nuclei and the body of the ameba so that finally eight motile amebae result The type of division of the nuclei in the cyst is exactly similar to that in the trophozoite so far as known

TABLE I INCIDENCE OF INFECTION WITH *Endamoeba histolytica* IN FOREIGN COUNTRIES

Observer	Localities	Number Examined	Percentage Positive
Allan and Charlotte	Near East troops	31 000	9 80
	Troops and civilians	000	10 50
	Western Front troops	5 000	8 90
Andrews	Fresnillo Mexico	302	12 90
Brug	Java natives	150	23 00
	Java Europeans	100	27 80
Carter Mackinnon Mathews and Smith	Mediterranean Area troops	4,068	12 10
	Hospital New Zealand	612	11 00
Connell	Yucatan	854	19 50
Dobell	Mediterranean Area	021	16 90
Dobell Gettings and Jepps	Dysentery convalescents in England	1 300	12 00
Epstein	Leningrad	1,404	25 30
	Kola Peninsula	900	60 60
	Azerbaidjan	1 146	32 50
	Georgia	570	17 0
	Turkestan	1 064	35 00
Faust	Peking		3 30
	Shansi		18 10
	Peking	60	20 00
Faust and Wassell	Yangtze Valley China general patient	319	1 30
	Intestinal diseases	57	50 87
Hiyeda	Manchuria	90	15 90
Jepps	Hospital patients, England	357	7 5
	Chinese and Malays	1 034	14 50
	Peking Chinese	816	29 50
Kessel and Svenson	Europeans	221	16 50
	Santa Marta	36	50 00
James	Hospital cases. India	1 163	10 10
MacAdam and Keelan	Hospital cases Mesopotamia	1 894	16 26
Mathews and Smith	Hospital patients England	450	1 50
	Army recruits	02	2 97
	Asylum patients	207	9 0
McCulloch	Kano	149	6 24
	Katsina	331	12 96
Philipschenco	Leningrad. Food handlers	400	22 75
Remlinger	Military Hospital Fez	1 620	40 00
Smith and Matthews	Hospital patients, England	250	8 00
Turner and Taylor	War hospital Enteritis group	327	15 40
Wenyon	British troops Egypt	199	5 30
	Native cooks Egypt	87	11 60
Williams and Thomas	Haiti domestics	109	50 00
Williams, Wildman and Curtis	Hospital patients Haiti	2 069	16 26
Young	Troops Brazil	252	27 50
Tao	China	9 533	20 40

known as amebic dysentery accompanied by lesions which are characteristic This is proven by the characteristic pathology associated with its presence, the experimental production of similar lesions in susceptible animals by the rectal injection of the trophozoites or by feeding the cysts of the parasite, by the occurrence in both naturally acquired and experimental infections in dogs and cats of a peculiar form of liver abscess associated with the presence of the ameba and finally by the production experimentally in man of the clinical picture of amebic dysentery by feeding the cysts, as demonstrated by Walker and Sellards in 1913 These observers fed 20 volunteers the cysts of *Endamœba histolytica*, of whom 18 later showed that ameba in the stools, and 4 of these later developed amebic dysentery

While it has been accepted for many years that *Endamaba histolytica* is the cause of amebic dysentery it has not been until recent times that it has been recognized that it is also the cause of much milder clinical pictures in which the symptoms are due to this parasite and that when the symptoms of dysentery develop the lesions produced by the ameba are well advanced and much ulceration is already present in the infected intestine As long ago as 1891 Dock demonstrated that ulceration of the intestine caused by this parasite might be present with no symptoms of dysentery, and his observation has been confirmed by Councilman and Lafleur (1891) Musgrave (1910), Bartlett (1917), James (1928) and Craig (1932) In many of these cases there is even no history of the occurrence of dysentery or diarrhea constipation being the condition complained of by the patient The recognition of these facts has lead to an entirely new conception of the importance of this ameba in human pathology and to the differentiation of the symptom complex known as amebic dysentery as only a portion of the clinical picture of amebiasis

Epidemiology

The geographical distribution of amebiasis has already been considered and is world wide although amebic dysentery occurs most frequently in the tropics and sub tropics

The incidence of infection with *Endamœba histolytica* varies greatly in different localities and largely depends upon the degree of sanitation and the social condition of the population That many individuals harbor this parasite without symptoms was first demonstrated by Walker and Sellards (1913), and all observers who have studied the subject are agreed that the incidence of infection in all localities is much greater than would be shown, if we depended upon the occurrence of dysentery or severe diarrheal symptoms in the diagnosis of the infection Numerous surveys of the incidence of infection with *Endamaba histolytica* have been made in various portions of the world, but because of differ

been found to vary greatly and in Table I are given the results of the principal surveys that have been made in various localities outside the United States

It will be noted that the percentage of infection with this parasite in different countries varies markedly and that it is highest in those countries in which there is a native population among which hygienic measures are poor or difficult of enforcement, and personal hygiene is little practiced

There have been many excellent surveys of the incidence of amebiasis in the United States and in Table II is given the results obtained in the most important of these surveys

It will be noted that Table II includes surveys showing a high incidence of infection with *Endamaba histolytica* as well as those showing a very low incidence and it is believed for this reason that it gives a fair picture of the incidence of amebiasis in the United States From the figures given in the table it is just to conclude that approximately between 8 to 10 per cent of the population of this country is infected with this parasite While the majority of those infected do not present symptoms of the infection that are of enough importance to attract attention the potential danger to health from infection is always considerable and renders amebiasis a public health problem of great importance in all countries where there is a high incidence of infection and of considerable importance wherever it occurs No one at present knows how much ill health and chronic invalidism are caused by amebiasis but enough is known to warrant proper treatment of every infection discovered whether clinical symptoms be present or absent

Since Table II was compiled an enormous amount of work as been done upon the incidence of amebiasis in the United States and at the date of writing (1945) the writer has data covering the examination of 118 156 persons in this country of whom 9 581 were found to be infected with *Endamœba histolytica* or 8 1 per cent If it be borne in mind that very many of these persons were examined only once for the parasite and often only one microscopical preparation was examined it is evident that the percentage must be much higher and recently Faust (1942) has stated that if several examinations be made with the improved methods now available the percentage of infection in the United States instead of being 10 per cent as stated by Craig may be as high as 20 per cent and that in poorly sanitated districts in the Western Hemisphere particularly in moist tropical regions an incidence of from 50 to 95 per cent is possibly a reasonable estimate'

In view of the constantly increasing tourist traffic between this country and Mexico it is important to remember that in Mexico the incidence of infection with *Endamœba histolytica* is high numerous surveys showing that it varies between 20 per cent in Mexico City to as much as 52 per cent in other localities Beltran (1944) recently has evaluated the surveys that have been made in Mexico and the figures given above are from his excellent contribution

TABLE II

RESULTS OF SURVEYS OF INFECTION WITH *Endamaba histolytica* IN THE UNITED STATES

Observer	Locality	Number Examined	Number Positive	Per Cent Positive
Wenrich Stabler and Arnett	Students Univ of Penn Phil	401	18	4 5
Boeck	From all parts of United States	8 209	333	4 1
Craig	Physicians all parts of U S	189	24	12 7
Cresswell and Wallace	Tacoma Washington	1 032	60	0 58
Faust	Rural Virginia	460	92	0 0
Faust	New Orleans La	1 100	158	13 7
Giffin	Mayo Clinic	1 ,00	,9	4 5
Hardy and Spector	Chicago Illinois	161	25	15 5
Hinshaw and Shavers	Philadelphia (patients)	358	4	1 1
Johnson and Iverson	San Francisco Cal (food handlers)	,47	22	3 0
Kofoid Kornhauser and Plate	U S Soldiers Home Service	5,6	25	4 3
	Foreign Service	2 300	297	12 8
Kofoid and Swezy	Students Univ of California	154	82	53 0
Magath and Ward	Mayo Clinic	457	36	7 9
Meleney	Rural Tennessee	4 987	861	17 3
Meleney Bishop and Leathers	Tennessee	20 23,	2 305	11 4
Milam and Meleney	Rural Community in Tenn	374	136	38 0
Bundesen Rawlings and Fishbein	Hotel in Chicago	364	86	23 6
Sanford	Mayo Clinic	5 000	535	22 5
Sistrunk	Mayo Clinic	145	25	17 2
Wight	Veterans Bureau	1 341	92	6 8
Andrews and Paulson	Baltimore Md	522	2	0 2
Reed and Johnston	San Quentin Prison Cal	1 000	92	9 2
Totals		51 634	5 277	10 2

ent technical methods employed it is difficult to evaluate accurately the results

Where only one microscopic examination of the stools has been made the number of positive results have been found much less than if several such examinations were made Likewise if concentration methods or culture methods be employed in making the surveys the number of positive cases will be greater, so that it is essential in considering the value of such surveys to know the technical methods that were employed in making them

In countries exclusive of the United States the incidence of infection has

Owing to the importance of the fly in the transmission of amebiasis the resistance of the cysts of *Endamœba histolytica* in the intestinal tract of these insects is important. Cysts adhering to the body of the fly are quickly killed by drying but it has been found that they may remain alive in the intestinal tract for a considerable time and be voided in a viable condition. Thomson and Thomson (1916) first demonstrated that the cysts could be found in the droppings of flies in a viable condition and Wenyon and O Connor (1917) found that they could remain alive in the intestine of the fly for 24 hours and in the feces of the fly for at least 16 hours after feeding upon contaminated material. Roubaud (1918) found viable cysts in the feces of flies as long as 48 hours after feeding upon contaminated material while Root (1921) found viable cysts in flies as long as 49 hours after ingestion. Wenyon and O Connor (1917) Buxton (1920) Frye and Meleney (1932) and others have found the cysts of *Endamœba histolytica* in flies collected around and in human habitations. Frye and Meleney finding them in the intestines of flies caught in 4 of 12 houses inhabited by carriers of this parasite.

The principal methods of transmission of amebiasis are through a contaminated water supply through the use of human excreta in the fertilization of garden vegetables or fruits through the handling of food or drink by individuals who are carriers of the ameba and through the droppings of flies that have fed upon material containing the cysts of this ameba.

Transmission by a water supply contaminated with feces containing the cysts is of frequent occurrence wherever there is no impounded and filtered general water supply and has been recognized from the very beginning of our knowledge of amebiasis. Water may also act as a most important transmitting agent when contaminated through cross-connections with sewers or unfiltered water supplies or through back syphonage where there is improper plumbing in hotels and other public buildings or even in the home. The 1933 epidemic of amebic dysentery originating in certain hotels in Chicago is a classical example of the importance of water in the transmission of amebiasis, where cross-connections exist between sewers and where improper plumbing is present. However it is in communities deriving their water supply from wells and springs situated near habitations and where soil pollution exists that water is most frequently the source of amebic infection and in rural districts contaminated water is very often the most important method of transmission of amebiasis. It has been invariably noted that the installation of a filtered public water supply in such communities has been followed by a very marked reduction in the number of infections with *Endamœba histolytica*.

In countries where human excrement is used for fertilizing purposes as in the Orient amebiasis is very frequently transmitted by the eating of uncooked vegetables from gardens so fertilized. This practice is not confined to the

The transmission of *Endamœba histolytica* from man to man is through the ingestion of food or drink contaminated by feces containing the cysts of this ameba. Only the cysts are infective to man as the motile trophozoites are destroyed by the normal gastric secretion, and it is important to remember that the stools of an acute case of amebic dysentery, which contain the motile trophozoites, usually are harmless so far as transmitting the infection is concerned, while formed stools containing the cysts are infective, should the cysts reach food or drink, the cysts resisting the acid of the gastric secretion. It thus follows that the patient suffering from acute diarrhea or dysentery produced by this parasite is usually non-infective, while he becomes infective when his symptoms disappear and his stools become semi-formed or formed. At this time he becomes a "carrier" of this ameba because the infective stage of the organism, the cyst, is then present in his stools.

As the resistance of the cysts of *Endamœba histolytica* is of supreme importance in the understanding of the epidemiology of this infection, the following data are of interest, the resistance of the cysts being ascertained by the use of staining and culture methods. It has been found that vital staining with a solution of eosin is useful for the reason that the dye does not penetrate the cyst unless death has occurred, but it is also true that some that are dead do not stain, so that the use of cultures is preferable in determining the resistance of the cysts to various agencies.

The work of numerous investigators has shown that the cysts will remain alive in the feces if they are kept moist and at room temperature, for from 9 to 21 days, while at lower temperatures they may remain alive for as long as 3 months. In water contaminated with feces containing the cysts, if fecal contamination is not excessive, the cysts remain alive at ordinary temperatures for from 1 to 5 weeks and in distilled water they will remain alive for from 10 to 20 days. According to Yorke and Adams (1926) the thermal death point of the cysts was 50° C (122° F) but they withstood a temperature of 45° C (112° F) for 30 minutes and 0° to 5° C (32° to 42° F) for 48 hours without injury. Drying kills the cysts almost instantly, thus proving that amebiasis can not be carried by dust as believed by some writers. Using the culture method for determining the death of the cysts, it has been found that they will resist a 1-2500 solution of bichloride of mercury for at least 30 minutes, a 1 per cent solution of carbolic acid for 30 minutes, a 0.5 per cent solution of formalin for 30 minutes, a 2 per cent solution of permanganate of potassium for 3 days, while the use of chlorine for water sterilization as usually applied is of no value in destroying the cysts of this ameba. The United States Army has perfected a method of sterilizing water in the field with chlorine by treating it first with a sufficient amount to kill the cysts, i.e. hyperchlorinating it, and then dechlorinating the water, but such a method has not yet been perfected for use in civil life.

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Orient but is apt to be indulged in wherever truck farms or gardens are operated by Oriental people

The contamination of food or drink by food handlers who are passing the cysts of *Endamœba histolytica* is believed to be the most common of all methods of transmission of amebiasis in regions where there is a properly guarded water supply and sanitation otherwise is excellent The writer has stated elsewhere (1934) that Food handlers in our hotels, restaurants, lunch counters, road side refreshment stands and other places, where food is handled and sold, are the chief source of amebic infection in well sanitated towns and cities in the United States and it may be stated that the contamination of food and drink handled by infected food handlers is practically a certainty unless the greatest care is taken regarding personal hygiene and the cleanliness of the hands of those who handle the food Cooks and mess attendants, salad makers, bread boys and even waiters are often efficient transmitters of amebiasis It should also be remembered that cooks and servants in private homes may be infected with this parasite and may infect whole families The writer has observed several instances in which infected cooks were responsible for the infection of several members of the family where they were employed'

Surveys made upon food handlers by numerous observers have shown that a considerable proportion of them are carriers of *Endamœba histolytica*, and this method of transmission of amebiasis must be a very important one

Transmission of amebiasis through the droppings of flies that have fed upon material containing the cysts of *Endamœba histolytica* is of importance wherever these insects are numerous and food or drink is not protected from them The writer (1916) has reported an epidemic of amebic dysentery which was apparently caused by the contamination of food by flies and this method of transmission becomes of great importance in military operations or civilian projects where large bodies of men are collected within a comparatively small space, and precautions regarding the breeding of flies are neglected, and food and drink are not screened against these insects

The possible importance of the existence of virulent or avirulent strains of *Endamœba histolytica* in the epidemiology of amebiasis is of interest, and some writers believe that strains of this parasite do exist which may live in the lumen of the intestine without invading the tissues while others believe that species exist indistinguishable in morphology from *Endamœba histolytica* but which are non pathogenic Sellards and Baetjer (1915) Meleney and Frye (1933) and others have apparently shown experimentally that strains of this ameba do vary in virulence while Brumpt (1928) Simic (1931–1933) and others believe that there is a distinct species of ameba which is indistinguishable in morphology from *Endamœba histolytica* but which is non pathogenic and Brumpt has named this ameba *Entamaba dispar*

That marked differences in virulence may exist between different strains of *Endamaba histolytica* has been proven by Meleney and Frye (1933-1935) Tobie (1940) and others Meleney and Frye (1935) studied several strains of this ameba as regards pathogenicity and found that they varied from very pathogenic strains to mildly pathogenic but that no strain examined by them failed to produce lesions and they concluded that any strain of *E histolytica* which is encountered in practice should therefore be considered as potentially dangerous to the person harboring it and to others to whom it might be transmitted Tobie (1940) examined sixteen different strains found in symptomless carriers of *Endamaba histolytica* as regards pathogenicity to dogs all of which produced lesions in these animals, although the lesions varied in severity with different strains Tobie s work is especially valuable because it demonstrated that even the strains found in carriers of *Endamaba histolytica* who had never presented clinical symptoms of their infection were pathogenic without exception and presumably capable of producing lesions in man Tobie concluded that from the evidence cited above it is highly probable that all carrier strains of *Endamaba histolytica* are pathogenic and that healthy human carriers as well as those individuals exhibiting clinical manifestations of the disease should be regarded as clinical cases

It is more than probable that rapid passage of strains of *Endamaba histolytica* through the human host may increase the virulence of such strains and this probably explains the excessive virulence of strains which have been observed in epidemics as in the Chicago epidemic of 1933

At the present time (1945) it may be stated that no conclusive evidence exists that any strain of *Endamaba histolytica* is non pathogenic to man but it is true that strains vary in virulence and that the resistance of the human host to the particular strain which may be present accounts for the variations in the clinical symptoms which may be observed or their entire absence In all cases in which the ameba are present and in which symptoms are absent lesions are occurring in the intestine even though microscopic in size and lowered resistance may bring about a clinical attack varying in symptomatology in accordance with the lack of resistance of the human host

The epidemic occurrence of amebic dysentery demands consideration for while this symptom complex of amebiasis usually occurs sporadically it may occur in epidemic form where heavy doses of the cysts are swallowed by a large number of individuals within a limited period of time Perhaps the most striking example of the epidemic occurrence of amebic dysentery is the Chicago epidemic of 1933 which was caused by the badly polluted water supply of two local hotels resulting in over 800 cases and over 50 deaths In this instance large numbers of people ingested water heavily polluted with fecal material containing the cysts of this ameba within a comparatively short period of

time with the result that many of them developed amebic dysentery, the incubation period varying from a few days to several weeks. This epidemic was investigated by a committee of experts and furnishes the first example of an epidemic of amebic dysentery due to a contaminated water supply occurring in a civil community. Epidemics of amebic dysentery have been reported among military personnel while in campaign or camp and the writer (1917–1934) has reported one occurring among United States troops camped at El Paso, apparently due to the contamination of food by flies. During this epidemic there occurred within a period of four months 118 cases of amebic dysentery, of which no less than 66 per cent developed within two months after the soldiers reached the camps in which the infection occurred. It is now thoroughly established that under favorable conditions epidemics of amebic dysentery may occur, and that the old idea that all epidemic dysentery is of bacillary origin must be abandoned.

The existence of *Endamaeba histolytica* as a parasite of the lower animals under natural conditions is of considerable importance in the epidemiology of amebiasis for the possibility of such animals acting as transmitters of the infection must be considered. The writer believes that the evidence now available demonstrates beyond doubt that this ameba does occur as a parasite in some of the lower animals for both morphologically and experimentally the organisms found in these animals are identical with *Endamæba histolytica*.

That certain species of monkeys are infected with an ameba, which is identical in morphology with *Endamæba histolytica* has been demonstrated by Castellani (1908), von Prowazek (191), Swellengrebel (1914), Eichhorn and Gallagher (1916), Brug (1923), Kessel (1927), Dobell (1931) and Knowles and Das Gupta (1934). Dobell (1931) was able to transmit the monkey ameba from monkey to monkey, to cultivate it in artificial media and concluded that neither in morphology, cultures nor pathogenesis does this monkey ameba differ from *Endamæba histolytica* of man, while Knowles and Das Gupta (1934) have produced infection in man with the cysts of the ameba found in monkeys, cysts which they regarded as *Endamaeba histolytica*. The writer believes that the ameba of the monkey identical in morphology with *Endamæba histolytica* undoubtedly is the latter organism and that in some regions monkeys may be instrumental in the transmission of amebiasis to man.

The rat has been found naturally infected with *Endamæba histolytica* by Lynch (1915), Chiang (1925), Andrews (1934), Andrews and White (1936) and Atchley (1936). Awakjan (1936) has infected kittens with the rat strain of *Endamæba histolytica* and produced typical lesions in the intestine.

The dog has been found infected with an ameba indistinguishable from *Endamæba histolytica* by Faust (1930) and Andrews (1932), while the pig has been found infected by Kessel (1928). The latter observation has not been confirmed.

These observations demonstrate that some of the lower animals are naturally infected with *Endamoeba histolytica* but their bearing upon the transmission of the infection of man still is undetermined It is more than probable that in some regions the infection of monkeys and rats may play an important rôle in transmission of the ameba to man but we have no definite data proving that the lower animals are important in epidemiology

The influence of age in the epidemiology of amebiasis is quite marked for the greatest number of infections are found between the ages of 0 and 45 but children of any age may become infected and amebic dysentery is not so very infrequently observed in children after the first two years of life while cases of of amebiasis in children presenting mild or no definite symptoms of the infection are frequently observed

The influence of sex also is well marked it being notorious that amebic dysentery is less frequently noted in women than in man while amebic abscess of the liver occurs very rarely in women Strong (1925) found that among 401 cases of amebic dysentery observed in Manila the ratios of men to women was as 4 1 to 1 while Tao (1931) found in a survey of 5 850 male Chinese 670 or 11 45 per cent infected with *Endamoeba histolytica* while of 2 595 female Chinese 208 or 8 02 per cent were found infected The writer believes that while amebiasis occurs more frequently in males than in females it does not indicate any immunity in the female but may be explained by lesser chance of exposure to infection on the part of the female This does not explain the relative freedom of females from the complication of amebic abscess of the liver, and no satisfactory explanation of this curious fact has yet been given by any students of amebiasis

The influence of race in the epidemiology of amebiasis is especially noted in the ratio between symptomless carriers of the ameba and those showing symptoms of the infection No race is immune to this parasite but it has been noted that native races living in localities where the infection is prevalent suffer less from clinical symptoms of the infection than strangers coming into the locality or whites who develop the disease The comparative freedom of native races from symptoms of amebiasis has been noted by all students of the subject and probably is largely due to a partial immunity to the effects of the parasite acquired by constant infection or reinfection A survey of adult natives living in regions where amebiasis is prevalent will always disclose a large number of individuals infected but amebic dysentery may be very rarely observed and other symptoms of amebiasis may be almost absent thus indicating that these people do not possess an immunity to the parasite but are partially immune to its effects

The influence of climate upon the transmission of amebiasis is of importance for a warm moist climate is more conducive to the spread of amebiasis

other things being equal, than a cool, dry climate The occurrence of amebic dysentery is markedly influenced by climate, and it is well known that this symptom complex of amebiasis is much more frequently observed in the tropics and sub tropics than in temperate or cold regions That this fact is largely explained by the effect of continued severe heat in reducing the resistance of the infected individual can not be denied, for the effect of removal from a tropical to a temperate climate of a patient suffering from amebic dysentery is always *marked by a great improvement in the symptoms and very often by an almost* miraculous return to health and strength The writer has observed scores of soldiers carried on litters aboard the transports at Manila suffering from severe amebic dysentery who without other treatment than rest in bed, recovered entirely from their symptoms before reaching San Francisco and were able to walk ashore at that port

No other explanation of such rapid improvement in these patients can be offered than the fact that the change from the hot depressing climate of Manila to the cool and bracing temperature of the ocean trip caused a marked increase in the natural resistance of the infected individuals and a temporary disappearance of the symptoms, due to the more rapid healing of the lesions produced by the parasite

The influence of immunity in the epidemiology of amebiasis is unknown That some individuals may be immune to invasion by *Endamaba histolytica* is evidenced by the fact that in regions where amebiasis is very prevalent some individuals apparently escape infection Whether this supposed immunity is a true immunity or due to lack of actual exposure to infection is unknown but the fact that so many individuals harbor the ameba without symptoms being produced speaks for at least a relative immunity to the effects of the infection which are evidenced in other individuals by the occurrence of definite symptoms Spontaneous disappearance of the amebae from the stools may occur in carriers without symptoms and even in individuals who have suffered from an attack of amebic dysentery

The observation that individuals may become immune to the strains of the malaria plasmodium present *in the locality in which they are living* while still susceptible to foreign strains of the organism is suggestive as regards amebiasis for it is not beyond reason to believe that natives in regions where amebiasis is common have developed at least a relative immunity to the strain of *Endamœba histolytica* there present while newcomers may develop symptoms of infection with the same strain *It is very evident that there is little or no* immunity following the cure of infections with this parasite, for reinfections are very frequently observed That the body does react to the invasion of the tissues by the ameba is demonstrated by the fact that the blood serum of in

fected individuals may contain complement fixing bodies as shown by numerous observers but nothing is known as to the relation that such bodies bear to immunity in amebiasis

PATHOLOGY

In discussing the pathology of amebiasis it is necessary to consider the lesions produced by *Endamœba histolytica* in the intestine in carriers of the infection as well as in patients suffering from amebic diarrhea or dysentery It is also necessary to describe the pathological lesions produced in the various organs of the body when invaded by this parasite and the general pathology of the blood in amebiasis

Endamœba histolytica is a tissue parasite living in the tissues of the body and producing lesions which are caused by the mechanical penetration of the tissues by the parasite and by the action of a cytolytic substance which it excretes Practically all authorities are agreed that the lesions of amebiasis are in large part due to cytolysis of the tissue cells but in practically every case there is some secondary invasion of the tissues by bacteria and how much of the characteristic pathological picture of amebiasis is due to the parasite alone or to mixed infection with various bacteria is problematical, the fact remains that the pathology of amebiasis and amebic dysentery is characteristic and easily differentiated from other pathological processes

Pathology of Amebiasis in Carriers

The pathology of amebiasis in carriers of *Endamœba histolytica* without symptoms as well as in those presenting only very mild symptoms of the infection has been investigated by Councilman and Lafleur (1891), Dock (1891) and Musgrave (1910) Bartlett (1017) Hiyeda and Suzuki (1931) and the writer (1934) and all of these observers have shown that microscopic ulcerations of the intestine exist in carriers while in many of them macroscopic ulcerations may be found within the bowel The microscopic and macroscopic appearances of the lesions in carriers do not differ from lesions observed in cases of amebic dysentery and it is abundantly evident that the pathology of amebiasis in carriers differs only in degree from that found in patients dying of acute amebic dysentery Extensive lesions may exist in the intestine without the production of appreciable symptoms but in all probability most symptomless carriers present only superficial areas of necrosis in the mucous membrane of the intestine very minute in size which heal almost as rapidly as they are produced Upon proctoscopic examination carriers sometimes show minute intensely inflamed areas in which necrosis has not occurred as well as minute

other things being equal, than a cool, dry climate The occurrence of amebic dysentery is markedly influenced by climate, and it is well known that this symptom complex of amebiasis is much more frequently observed in the tropics and sub tropics than in temperate or cold regions That this fact is largely explained by the effect of continued severe heat in reducing the resistance of the infected individual can not be denied, for the effect of removal from a tropical to a temperate climate of a patient suffering from amebic dysentery is always marked by a great improvement in the symptoms and very often by an almost miraculous return to health and strength The writer has observed scores of soldiers carried on litters aboard the transports at Manila suffering from severe amebic dysentery who without other treatment than rest in bed, recovered entirely from their symptoms before reaching San Francisco and were able to walk ashore at that port

No other explanation of such rapid improvement in these patients can be offered than the fact that the change from the hot, depressing climate of Manila to the cool and bracing temperature of the ocean trip caused a marked increase in the natural resistance of the infected individuals and a temporary disappearance of the symptoms, due to the more rapid healing of the lesions produced by the parasite

The influence of immunity in the epidemiology of amebiasis is unknown That some individuals may be immune to invasion by *Endamaba histolytica* is evidenced by the fact that in regions where amebiasis is very prevalent some individuals apparently escape infection Whether this supposed immunity is a true immunity or due to lack of actual exposure to infection is unknown, but the fact that so many individuals harbor the ameba without symptoms being produced speaks for at least a relative immunity to the effects of the infection which are evidenced in other individuals by the occurrence of definite symptoms Spontaneous disappearance of the amebae from the stools may occur in carriers without symptoms and even in individuals who have suffered from an attack of amebic dysentery

The observation that individuals may become immune to the strains of the malaria plasmodium present in the locality in which they are living while still susceptible to foreign strains of the organism, is suggestive as regards amebiasis for it is not beyond reason to believe that natives in regions where amebiasis is common have developed at least a relative immunity to the strain of *Endamaba histolytica* there present while newcomers may develop symptoms of infection with the same strain It is very evident that there is little or no immunity following the cure of infections with this parasite, for reinfections are very frequently observed That the body does react to the invasion of the tissues by the ameba is demonstrated by the fact that the blood serum of in

extending throughout the large intestine but most severe and numerous below the ileo-cecal valve and in the rectum, while in the remaining 9 lesions were found in the rectum only with scars of healed lesions below the ileo-cecal valve While it is true that the lesions in amebic dysentery are almost invariably limited to the large intestine, the writer has observed amebic ulceration of the lower portion of the ileum in 6 cases and such instances have been reported by other observers

The report by Wooley and Musgrave (1904) of the location of ulcerations in 100 cases of amebic dysentery autopsied in Manila showed that the entire large intestine was involved in 87 cases the ulcerations were confined to the cecum and ascending colon in 5 to the transverse colon in 1 while in 7 the location is not stated In 25 carrier cases dying of other diseases the ulcerations were confined to the cecum and ascending colon in 11 cases to the descending colon the sigmoid and the rectum in 8 cases, and were distributed throughout the bowel in 6 cases Thomson and Robertson (1929) quote Bartlett as stating that in an analysis of 56 cases of fatal amebic dysentery the lesions were found throughout the large intestine in 9 or 51 7 per cent throughout the colon but not in the rectum in 9 or 16 per cent, in the descending colon and rectum only in 6 or 10 7 per cent in the colon only in 2 or 3 5 per cent in the cecum ascending colon and sigmoid in 6 or 10 7 per cent and in the cecum and ascending colon only in 4, or 7 8 per cent

From these data it is evident that the location of the lesions in amebic dysentery varies greatly in individual patients but it is also evident that ulcerations are most frequently encountered in the cecum ascending colon sigmoid and rectum and that the longer the infection has lasted the greater the amount of pathological change

The *macroscopic appearance* of the large intestine in amebic dysentery varies greatly with the extent of the invasion of the tissues by the ameba Externally it usually appears of a greyish white color with areas of discoloration marking the situation of ulcerations which have penetrated to the muscular coats and in some instances black irregular areas may be observed due to gangrene of the intestine Adhesions frequently exist between the large intestine and coils of the small intestine and in cases where many attacks of dysentery have occurred there may be marked thickening of the walls of the intestine and contractures brought about by hypertrophy of the submucous and muscular coats and narrowing of the lumen during the healing of the ulcerations

Internally the large intestine presents the lesions which are characteristic of amebic dysentery varying from minute just visible necrotic areas to large ulcerations sometimes girdling the gut and penetrating to the muscular coat

The first lesion observed in amebiasis and in symptomless carriers often the only observable lesion is a cytolysis and necrosis of the superficial cells of the

ulcers, superficial in character, scrapings from which will show the presence of trophozoites of *Endamœba histolytica* More rarely extensive ulceration may be found in carriers without symptoms, and liver abscess is observed sometimes in carriers who have never suffered from diarrhea or dysentery

The pathology of amebiasis in individuals who have had repeated attacks of mild or severe diarrhea due to *Endamœba histolytica* is that mentioned as occurring in symptomless carriers to which is added the pathology characteristic of the milder grades of amebic dysentery Areas of superficial necrosis and well marked and typical ulcerations varying in size from those just visible to the naked eye to ulcers of considerable size, are commonly found in the intestine in such cases and as the lesions are identical in morphology with those encountered in amebic dysentery their description will be found in the discussion of the pathology of that condition

The Pathology of Amebic Dysentery

The pathology of amebic dysentery has been thoroughly studied by many observers and excellent and detailed descriptions exist in the literature of all of the lesions which have been found at autopsy in patients dying of this infection More recently, many investigators have described in great detail the lesions which occur in experimental animals, but it is a fact that nothing of significance has been added to our knowledge of the pathology of amebiasis by such studies and very erroneous conclusions have sometimes been drawn regarding the pathology of amebiasis in man from the study of lesions caused by *Endamœba histolytica* in experimental animals

The lesions of amebic dysentery are absolutely characteristic, and a diagnosis between this condition and other forms of dysentery, with the exception of dysentery due to *Balantidium coli* can be easily made by an inspection of the infected intestine alone The bacillary dysenteries which are most apt to be confused pathologically with amebic dysentery are easily distinguished by the morphology of the lesions even in the more chronic forms of bacillary dysentery in which the ulceration approaches more closely that found in amebic dysentery

Location of the Lesions — The lesions of amebiasis and amebic dysentery are found most frequently in the ileo-cecal region and the rectum and in mild infections may be entirely confined to these regions or to the ileo-cecal region alone The rectum usually shows ulcerations, if the infection has lasted for a considerable period of time but not infrequently the region just below the ileo-cecal valve is the only portion of the intestine showing ulceration In a series of 78 fatal cases of amebic dysentery observed and reported by the writer (1934) lesions were observed below the ileo-cecal valve in the descending colon just above the rectum and in the rectum in 57 cases, in 12 cases there were lesions

while larger ulcers are more irregular and may sometime encircle the bowel, due to coalescence of two or more large ulcers In the less severe cases of amebic dysentery ulcers are found in which the edges are not undermined but raised slightly *from the surface of the bowel, and the floor is formed by the sub* mucous coat of the intestine Such ulcers are almost invariably present along with the irregular ulcers in severe cases but they exist almost alone in the mild cases of amebic dysentery

In the so-called fulminant type of amebic dysentery which the writer believes to be always due to a mixed infection with bacteria especially the dysentery bacilli the entire large intestine may present a gangrenous appearance large areas of the mucous membrane being inflamed and gangrenous, while other areas are covered with both superficial and deep ulcerations

In patients who have had repeated attacks of dysentery the healing of the ulcerations results in the formation of scar tissue which again may result in contractures of the lumen of the bowel Healing occurs from the periphery of the ulcer and in the smaller ulcers there is little or no formation of fibrous scar tissue but in the large ulcers there is hypertrophy of the connective tissue and the formation of dense fibrous scars replacing the mucous membrane of the intestine

In some cases where ulceration has been extensive, the interior of the intestine may be covered with scar tissue and in this way most of the mucous membrane may be replaced by fibrous tissue a condition of importance in understanding the clinical symptoms present in patients who have suffered and recovered from chronic amebic dysentery

The lesions of amebic dysentery which are characteristic and diagnostic are the nodular elevations situated at the summits of the folds of the mucous membrane containing gelatinous cytolysed material and trophozoites of *Endamœba histolytica* ulcers with thickened undermined edges which present a shaggy appearance due to shreds of cytolysed and necrosed tissue hanging from them and sinuses leading from ulcer to ulcer beneath the mucous membrane of the intestine

It has already been stated that rarely amebic ulcerations are observed in the lower portion of the ileum The ulcers in this region usually are of superficial character small in size and the floor is formed by the mucous or submucous coat of the intestine

Involvement of the appendix is probably much more frequent in amebiasis than is usually believed and typical amebic ulcers sometimes are observed in this organ In such cases the appendix is edematous and hypertrophied and small oval or round ulcers with slightly undermined edges are observed James (1928) found the appendix showing pathological lesions in 33 3 per cent of cases of amebiasis coming to autopsy in Panama

mucous membrane visible as minute pin point areas surrounded by edema and hyperemia In cases of acute or chronic amebic dysentery these minute lesions may be seen scattered between larger ulcerative lesions and the nodular lesions common in this infection

The early stage of amebic dysentery is characterized by a lesion which is known as the nodular lesion, the surface of the intestine showing small nodular elevations which, when incised are found to consist of flask shaped areas of cytolysis and necrosis containing a yellowish or brownish yellow glairy substance composed of cytolysed tissue in which actively motile trophozoites of *Endamœba histolytica* may be demonstrated The nodular elevations are surrounded by hyperemia and edema and are situated in the mucous and upper portion of the submucous coats of the intestine The process of cytolysis extends laterally and downward, while the necrosed covering of the nodule disappears, and in this manner definite ulcerations are produced The floor of such ulcers usually is formed by the submucous coat of the intestine but gradually the muscular coats become involved, and the ulceration may even penetrate to the peritoneal coat or through the latter The edges of the ulcers are ragged, undermined in many instances, and motile trophozoites may be found in material obtained from scrapings of the floor or edges of the ulcerations The ulcers spread laterally as well as downward, and the lateral extension results in sinuses beneath the mucous membrane which may connect the ulcerations or terminate in the mucous or submucous coats of the intestine The ulcerations, when small may present a punched out" appearance and often because of lateral extension and long, narrow openings, resemble a button hole and are known as button hole ulcers', a type of ulceration occurring only in amebic dysentery

The invasion of the mucous and submucous coats in a lateral direction, as above noted results in the formation of sinuses beneath the mucous coat, which when opened are found to contain the same glairy, mucoid material found in the flask shaped nodules and in severe infections the coalescence of ulcerations and sinuses results in large irregular ulcerations and sloughing of considerable areas of the mucous and submucous coats of the intestine, with hemorrhage In such cases the so called buffalo skin" appearance so characteristic of the most severe type of amebic dysentery is observed the intestine presenting large ulcerations with irregular shaggy edges with fibrinous masses of necrosed tissue hanging from the interior, the whole picture resembling a buffalo hide

Typical amebic ulcerations are characterized by great variation in size and depth The edges frequently are undermined and present a ragged appearance while the floor may be rough or smooth and usually is covered with necrotic tissue, pus and blood The smaller ulcers usually are oval or round in shape

SYMPTOMATOLOGY

From the description of the pathology of amebiasis and amebic dysentery it is evident that the symptoms which accompany infection with *Endamœba histolytica* must vary greatly and clinically they do vary from mild indefinite symptoms connected with the gastrointestinal tract to those of the most fulminant attack of amebic dysentery or those which are present in amebic abscess of the liver brain or other organ

The *incubation period* as regards the appearance of symptoms of the infection varies so greatly that one is hardly justified in speaking of such a period in amebiasis An infected individual may go for weeks months or even years with no symptoms which can be proven to be due to the presence of the parasite in the intestine while in others the most severe symptoms of amebic dysentery may appear after an incubation period of only a few days To undertake to state the usual period of incubation in this infection is an impossibility in most instances although during epidemics it is possible to arrive at a probable period under the conditions in which epidemics may occur The period of incubation in the human volunteers infected with this ameba by Walker and Sellards (1913) was found to be 0 57 87 and 95 days that is this number of days passed before symptoms of dysentery appeared in the four men who developed this condition However of the 20 volunteers fed with cysts of the ameba, no less than 18 became parasitized the pre patent period or period between the time of feeding and the appearance of tropnozoites or cysts in their stools varying from 1 to 44 days the average being 9 days It is evident that in the four men developing dysentery the parasite appeared in the stools long before the symptoms of dysentery occurred

In an epidemic of amebic dysentery the writer observed at El Paso and reported in 1916 it was determined that the symptoms of dysentery developed within 90 days after the infected individuals reached the infested camps Thus in the 100 cases studied as regards the period of incubation 36 or 36 per cent developed symptoms of amebic dysentery within 30 days after arrival, 66 or 66 per cent within 60 days after arrival and 90 or 90 per cent within 90 days after arrival In this series of cases it is probable that these figures approximately represent the real period of incubation but among these cases were some who developed amebic dysentery within a week after arrival and as long as one year after arrival thus indicating the great variability in the period of incubation

The 1933 Chicago epidemic of amebic dysentery was characterized in many cases by the extremely short period of incubation probably due to the excessive number of cysts ingested in a badly polluted water O Connor (1934) states that in some of the Chicago cases symptoms of dysentery developed within

The *microscopic pathology* of amebic dysentery is as characteristic as the macroscopic which has just been described In sections of the invaded intestine trophozoites of *Endamaba histolytica* may be seen collected in nests or distributed singly in any of the coats of the intestine but most frequently in the mucous sub mucous and muscular coats The absence around the organisms of round cell infiltration and other evidences of inflammation in uncomplicated cases and the presence of cytolysed tissue remains demonstrates beyond question that the damage caused by the organism is produced by dissolving the tissue which it invades It is only in locations where the amebic invasion is complicated by the presence of bacteria that one finds the usual indications of inflammation i e the presence of marked cellular infiltration with neutrophilic leukocytes lymphocytes and connective tissue cells Areas showing such a mixed infection will be found in most sections of the diseased tissues, for a pure amebic infection is impossible

The trophozoites of *Endamœba histolytica* may be seen in and between the glands in the mucous coat, in all parts of the sub mucous and muscular coats and within lymph spaces and blood vessels They are always surrounded by an area of cytolysed tissue indicated by granular debris, remains of tissue cells and amorphous material staining poorly The characteristic microscopic pathology of amebiasis consists in the presence in the invaded tissues of the trophozoites and the cytolysis of the tissue in which they may be present

The tissues surrounding the cytolysed areas in a pure amebic infection do not show infiltration with neutrophilic leukocytes but often present a slight infiltration with mononuclears and connective tissue cells Sections of the diseased intestine demonstrate that the invasion of the tissues begins by a cytolysis and penetration of the superficial layer of the mucous coat and extends from that location laterally and downward until all of the coats of the bowel may be involved

In experimental animals the lesions produced by infection with *Endamœba histolytica* differ considerably from those which are observed in natural infections in man In the smaller laboratory animals as the rabbit and guinea pig, the lesions are granulomatous in character while in the kitten there are produced superficial ulcerations the infection usually being rapidly fatal in these animals In the dog as shown by Faust and Kagy (1934) the lesions are very similar to those occurring in man and quite different from those which are commonly observed in kittens Flask shaped lesions and deep ulcerations are observed in these animals and it is evident that the process of invasion of the tissues is similar to that which occurs in man

The *pathology of the complications of amebiasis*, as amebic abscess of the liver, amebic invasion of the skin, etc, will be considered in discussing the complications

The symptomatology of amebiasis in carriers is confined almost entirely to the gastrointestinal tract and the nervous system Some few authorities claim to have demonstrated that *Endamœba histolytica* sometimes causes lesions in the eye and other organs of special sense but the experience of the writer does not support this assumption Among the most important symptoms noted in carriers of *Endamœba histolytica* are the following

Pain in the abdomen or a sense of discomfort in that region, is almost invariably present varying from a dull aching discomfort to attacks of acute abdominal colic The location of the pain varies greatly but is most generally felt in the lower bowel although frequently in the hepatic and gall bladder region and in the cecal and appendicular region The pain frequently simulates very closely that present in chronic appendicitis or cholycystitis and many carriers have been operated upon because of the similarity of their symptoms to those of a chronic appendicitis Epigastric pain may be present but is rare as compared with abdominal pain

One of the most frequent symptoms of amebiasis in carriers is *abdominal distension* occurring immediately or a short time after eating and accompanied by eructations of gas and often by abdominal pain In many individuals the distension is slight and unaccompanied by pain so that this symptom may be overlooked by the patient

Constipation is present very frequently in carriers and may alternate with short periods of very slight diarrhea One should remember that in carriers constipation is the prevailing condition instead of diarrhea as thought by many clinicians and that a history of constipation is really of more diagnostic importance in these mild cases of amebiasis than one of diarrhea Diarrhea when present usually occurs suddenly after a period of constipation and frequently at night the patient being awakened by abdominal pain followed by the passage of two or three large diarrheal stools after which the pain disappears and the diarrhea ceases Such attacks of diarrhea seldom persist for more than a few hours but diarrheal attacks may occur in which for a day or two there may be from three to four semi fluid stools daily succeeded by a period of normal movements or by constipation Considerable mucus may occur in the diarrheal stools but blood usually is absent while trophozoites of *Endamœba histolytica* may be numerous Many individuals who are carriers of this ameba do not suffer from either constipation or diarrhea under ordinary conditions but in such persons the use of alcoholic drinks or over-eating frequently results in an attack of diarrhea

In carriers a *capricious appetite* is observed very frequently the individual at one time having a ravenous appetite and at another almost complete loss of appetite Anorexia is a common symptom at times while nausea and vomiting may occur

4 days after exposure, and that in the majority of the cases that he studied the incubation period before the development of dysenteric symptoms varied between 10 and 18 days

The shorter periods of incubation as reported by O'Connor and the writer seldom occur in amebic dysentery and are either due to overwhelming doses of the infective cysts or to greatly decreased resistance upon the part of the infected individual or to both It is the experience of all who have studied amebiasis that the symptoms of dysentery, if occurring at all, usually do so after the cysts of *Endamœba histolytica* have been present in the stools for weeks or months It is thus evident that the period of incubation can not be accurately stated but varies very greatly in different individuals

The *symptomatology* of amebiasis is so protean in character that it is necessary to divide the infections into several classes according to the presence or absence of certain symptoms For convenience of description the writer has divided individuals infected with *Endamœba histolytica* into four classes, but it should be remembered that these classes tend to merge into one another Class I includes the so called "healthy" carriers of the parasite, Class II, those who present mild indefinite symptoms connected with the gastrointestinal and nervous systems and who are usually considered as carriers, Class III, those who in addition to the symptoms present in individuals in Class II, suffer from recurring attacks of diarrhea, and Class IV, those suffering from acute or chronic amebic dysentery

Symptoms in Carriers

Symptoms in individuals in Class I are either absent or so indefinite and so mild that the infection is not suspected and even upon inquiry either no symptoms can be elicited or they are so slight as to be of no consequence These so-called "healthy carriers" of *Endamœba histolytica* comprise at least 50 per cent of those infected in temperate and cold regions, but it should be remembered that symptoms may develop at any time or an amebic abscess of the liver appear although no history of diarrhea or dysentery may be obtainable

The symptomatology presented in individuals comprised in Class II is of special interest because the majority of such individuals are usually considered as "healthy" carriers of *Endamœba histolytica* The writer believes there is no such thing as a healthy carrier of this parasite, for even in the absence of symptoms lesions are always present in the intestine, although they may be microscopic in size and heal rapidly It has been his experience that from 50 to 65 per cent of individuals showing cysts of this ameba in the stools have symptoms which are due to the presence of the parasite, although many of these individuals consider themselves to be in good health

vaso-motor system is evidenced by the sudden *flushings of the skin* accompanied by localized *perspiration*, which are often observed in carriers of *Endamœba histolytica*

Loss of weight is observed very frequently in carriers and most carriers are below normal in weight The writer has frequently found that individuals below normal in weight without any apparent reason are carriers of *Endamœba histolytica* and that elimination of the infection resulted in a prompt gain in weight to normal or about normal limits Individuals infected with this parasite may present periods of constant loss in weight succeeded by others in which there is some gain apparently depending upon the variations in resistance of the individual to the infection

Tenderness of the abdomen upon palpation is noted in many carriers and owing to its frequent location in the appendicular region has led frequently to an erroneous diagnosis of chronic appendicitis Tenderness and soreness usually is localized around the appendix in the ileo-cecal region or over the ascending and descending colon Tenderness over the region of the gall bladder is not unusual and the diagnosis of chronic cholecystitis sometimes is made, but that there is a form of cholecystitis due to the invasion of the gall bladder by *Endamœba histolytica* is doubtful Tenderness over the liver is observed sometimes in carriers and it should never be forgotten that amebic abscess of the liver may occur in individuals who have never suffered from diarrhea or dysentery

From the description of the symptomatology of amebiasis in carriers it is evident that the same symptoms may occur in other infections and diseases of the gastrointestinal tract and that single symptoms or any combination of these symptoms is not pathognomonic of this condition The symptoms mentioned are merely suggestive and if they occur should always lead to a careful examination of the feces for the ameba It is often surprising to discover that patients who have made the rounds of gastroenterological clinics and have been examined for practically every other known disease condition of the gastrointestinal tract are really suffering from amebic infection and that the symptoms all disappear after appropriate treatment

Symptoms in Patients with Diarrhea

The symptomatology of amebiasis in individuals who may be placed in Class III or those suffering from repeated attacks of diarrhea are identical with those described in the foregoing class i e carriers with indefinite symptomatology except that well marked periods of severe diarrhea occur usually alternating with periods of constipation The diarrhea usually is accompanied by colicky pains in the abdomen and may last for several days or even weeks

Headache of a dull, boring character is a very frequent symptom in carriers and usually is frontal in location, although it may be occipital The patient frequently awakes with a headache which passes off during the day, or it may begin at any time of the day and persist until evening Headache may occur every day or only appear at intervals of a few or many days, while in the headache free intervals the individual may feel normal, or there may be a persistent heavy feeling in the head with areas of hyperasthesia of the scalp The *memory* may be poor, and there is lack of ambition and difficulty in mental concentration, while nervous irritability is frequently observed *Insomnia* is rarely noted, but disturbed slumber is common, the individual awaking several times during the night Many carriers complain of feeling sleepy during the day or of a dull listless feeling after the mid day meal which persists for the remainder of the day, usually accompanied by a headache of slight severity

One of the most common symptoms noted in carriers is *muscle ache* especially in the muscles of the legs This usually is most noticeable upon awaking in the morning and disappears in an hour or two after arising Muscle ache may also occur in the muscles of the arms and back, and the muscles may feel sore upon pressure Some carriers complain of a dull ache in the lower abdominal muscles which may be almost constant in character

A *sub normal temperature*, especially in the early morning, is one of the most common symptoms of amebiasis in carriers Such individuals usually present a temperature varying between 36° C (97° F) in the morning to 37° C (98 F) at evening but many show a much lower morning temperature and temperatures of 35 5° C (96 5 F) and 36° C (97° F) are not infrequently observed

Fever is very rarely observed in carriers, but the writer has seen cases in which there was an evening rise of temperature of one degree persisting for weeks and followed by a normal temperature In such cases one should be suspicious of hepatic involvement and the formation of an amebic liver abscess

A *weak heart action* is a common symptom, the pulse being irritable and of decreased tension Arrhythmias are frequent, and slight exertion is followed by a rapid pulse which may intermit Carriers frequently complain of palpitation, and attacks of tachycardia may occur Dyspnea and dizziness are sometimes observed and individuals who are carriers of *Endamœba histolytica* frequently are sedentary in their habits because of the unpleasant effects of exercise upon the heart Wilson (1923) who has made a study of the heart in amebiasis, believes that the heart symptoms are caused by the absorption of toxins which act directly upon the cardiac vagus, increasing its irritability and producing a dislocation of the control mechanism of the heart (and of the vaso motor system)', resulting in the organ accelerating upon slight provocation with the occurrence of palpitations, pain, dyspnea and dizziness The disturbance of the

early symptoms of amebic dysentery usually colicky in character and located in the right iliac region or in the lower abdomen The pain is most noticeable just before the evacuations sometimes being very severe but disappearing after the bowel movement is completed In many of the milder cases abdominal pain is slight consisting of a few cramp-like pains occurring just before the passage of the stools, while in a few cases no abdominal pain is noticed Usually there is considerable tenderness in localized areas over the abdomen, especially in the right iliac region the ileo-cecal region over the sigmoid and the descending colon Muscular rigidity may be present and rarely the tenderness is so general as to suggest peritonitis The abdominal pains continue throughout the attack, gradually disappearing as the stools become normal in number and appearance

Fever — In mild attacks of amebic dysentery fever is not a common symptom in uncomplicated cases but in severe attacks and especially in the fulminant infections fever is almost always present Fever is more frequently present in amebic dysentery occurring in the tropics than in temperate regions but as shown by Futcher (1903) in an analysis of 120 cases of amebic dysentery observed at the Johns Hopkins Hospital fever usually was present at the onset and during the acute symptoms disappearing as the condition became chronic in character The writer has noted that a temperature varying between 37 5° C to 39 C (100–102° F) is often observed in patients who are very acutely ill at the onset but it has not been the writer's experience that most cases of amebic dysentery in temperate regions are characterized by fever However it should be emphasized that the old idea that amebic dysentery is never accompanied by fever is incorrect and the presence of fever does not necessarily indicate that the dysentery is of bacillary origin as is stated in some works upon the subject Fever may be present in uncomplicated cases of amebic dysentery during the onset or at some time during the course of the infection but it is the exception rather than the rule in the vast majority of cases unless very severe or fulminant symptoms are present when fever is a common symptom In chronic amebic dysentery fever seldom is noted during the recurrences of dysentery and the temperature often is subnormal in such infections

A *chill* may occur during the onset especially in fulminant cases and chilly sensations or chills may occur during the attack if it be a severe one and accompanied by marked prostration

The Bowel Movements — The bowel movements vary in number with the severity of the attack In mild attacks so frequently observed in temperate regions the number of bowel movements seldom exceeds 6 or 8 a day while in the more severe cases in cooler climates the number is usually from 10 to 15 a day In the tropics the number of bowel movements averages from 15 to 20 a day in a case of average severity In the very severe and fulminant cases

The attack usually occurs suddenly but may be preceded by several days in which the stools are increased in number and are mushy in consistence The stools during the diarrheal attack may vary from 3 to 12 or more during 24 hours and usually are semifluid in consistence, bile stained and contain considerable mucus and microscopically blood corpuscles usually are present in small numbers Motile trophozoites of *Endamœba histolytica* are present in the stools and considerable degenerated intestinal epithelium The attacks of diarrhea may recur at frequent intervals for months, or they may disappear for long periods of time only to recur later In a few cases observed by the writer an almost constant diarrhea was noted for several weeks, the stools varying in number from two to as many as six per day and containing much mucus and sometimes a trace of blood Such infections are on the borderland between amebic diarrhea and amebic dysentery, and most of them eventually will present the clinical picture of amebic dysentery if untreated

In patients suffering from amebic diarrhea the occurrence of a slight evening temperature of tenderness over the liver and of a leukocytosis of between 12 000 to 16 000 leukocytes per cubic mm suggests the development of an amebic abscess of the liver and such symptoms, in the experience of the writer, justifies the use of emetine hydrochloride which is most efficient in preventing this condition

Symptoms in Patients with Amebic Dysentery

The symptoms of amebiasis in patients belonging to Class IV, or those developing amebic dysentery, are those which are characteristic of acute or chronic amebic dysentery The incubation period of this symptom complex has been discussed already and the symptoms vary greatly in severity from mild attacks characterized by a few mucoid and bloody stools per day to fulminant infections characterized by very numerous stools consisting almost entirely of blood and mucus and by extreme prostration and a fatal ending within a few days In the tropics the more severe and fulminant types of amebic dysentery are observed, while in cooler regions the usual type is a mild one and spontaneous recovery from the attack is the rule

The onset of the symptoms of amebic dysentery usually is sudden, but in the temperate regions there often is a history of previous attacks of diarrhea or of the symptoms noted in carriers In many cases the patient may have suffered for a few days from diarrhea which is succeeded by the appearance of much blood and mucus in the stool and the other symptoms of dysentery The symptoms which are most frequently noted in attacks of amebic dysentery are the following

Abdominal Pain — Pain in the abdomen is almost invariably one of the

the descending colon After repeated attacks of dysentery the bowel wall becomes greatly thickened owing to the formation of fibrous tissue in the healing of the ulcers, and frequently portions of the large intestine may be very easily palpated and the course of the intestine accurately mapped out by palpation

The Blood in Amebiasis

The blood picture in amebiasis is not distinctive, but certain changes occur which vary with the stage of the infection

In *carriers* without symptoms or with mild symptoms there is frequently a slight degree of *anemia* the erythrocyte count averaging about 4,000 000 to 4 500 000 cells per cu mm the leukocyte count being normal and the hemoglobin averaging 10 to 20 points below normal During the *acute attack* in amebic dysentery the erythrocyte count averages between 4 000,000 to 5 000 000 The average hemoglobin estimate is between 65 and 75 per cent, and the leukocyte count averages between 10,000 and 12 000 per cu mm If the bowel movements are numerous and profuse the erythrocyte count may be higher than 6 000 000 per cu mm due to the loss of fluids and concentration of the blood The leukocytes in most uncomplicated cases average about 10,000 per cu mm but may be as few as 7,000 or as many as 20,000 per cu mm If a *liver abscess* is present or is forming the leukocyte count averages between 16 500 and 18 000 per cu mm but may be much higher counts as high as 40,000 to 50 000 having been observed In *chronic amebic dysentery* there may be a marked reduction in the erythrocytes the count averaging between 3,000,000 and 3 500 000 per cu mm, while the leukocytes are slightly increased in number and the hemoglobin reduced to 60 per cent or even lower if the infection has lasted for a long time In chronic cases a leukocytosis above 15 000 per cu mm is suggestive of the presence of a liver abscess There is nothing diagnostic about the *differential leukocyte count* in amebiasis In carriers the differential count is normal in amebic diarrhea and mild cases of amebic dysentery it may show a slight increase in neutrophilic leukocytes and in monocytes while if an amebic abscess is forming or is present usually there is a *marked increase in neutrophilic leukocytes In some cases of amebiasis an* eosinophilia of very slight degree may be present but eosinophilia of any extent is almost invariably due to some complicating condition or infection

COMPLICATIONS

Endamœba histolytica is not confined to the tissues of the intestine but may *invade other tissues of the body giving rise to numerous complications* which will now be considered

the bowel movements may number from 30 to 40 a day, and prostration is very rapid In order to avoid repetition the macroscopical and microscopical character of the stools in amebic dysentery will be discussed in the section treating of Diagnosis

Tenesmus is not as marked in the average case of amebic dysentery as in bacillary dysentery but it may be very severe in cases in which there is much rectal ulceration or in the fulminant infections The presense of ulceration in the rectum always causes more or less tenesmus, and it is in those cases in which marked rectal ulceration exists that the tenesmus is greatest In many mild cases of amebic dysentery tenesmus may be practically absent or so slight as to cause little discomfort but in the average case tenesmus is present and the discomfort is in ratio to the number of bowel movements and the amount of rectal ulceration

Emaciation does not occur during a primary attack of mild amebic dysentery, although there is always some loss in weight, but in severe or fulminant infections it may be very rapid, and in a few days the patients may lose so much weight as to appear much emaciated However, it is in the old, chronic cases of amebic dysentery that emaciation is most marked If the bowel movements are very numerous the patient becomes quickly emaciated during the acute exacerbations and seldom recovers the weight lost during the intervals, so that eventually great emaciation results

Symptoms of Chronic Amebic Dysentery

The symptoms of chronic amebic dysentery usually are preceded by a period succeeding the primary acute attack, of absence of symptoms or of mild rather indefinite symptoms consisting of slight diarrhea and gastro-intestinal disturbance The primary attack, unless successfully treated, or spontaneous recovery occurs is always followed by other attacks of dysentery, in which the symptoms are similar to those observed during the primary acute attack and which have already been discussed In such cases recurring attacks of dysentery may occur for years and the patient be reduced to a state of chronic invalidism

As in the primary acute attack, *fever* is not always present, but a temperature between 37 2 and 38 5° C (99 5–101° F) frequently is present during the acute exacerbations, but usually the temperature does not exceed 38° C (100° F) If a daily temperature develops persisting after the acute dysenteric symptoms have subsided, it is very significant of a beginning amebic abscess of the liver *Abdominal pain* and *tenderness* are always present during the acute exacerbations of dysentery, and between the attacks there is soreness and tenderness over localized areas of the abdomen usually over the cecum, the ascending colon or

years of age Roger s experience has been that of practically all observers, so that it may be stated that this complication is essentially one of adult life

Other predisposing causes of abscess of the liver are excessive indulgence in alcohol exposure starvation or improper food mental stress, traumatism over the liver and any condition which markedly lowers the normal resistance of the individual

Dysentery and Abscess Formation — While the majority of patients who develop an amebic abscess of the liver have a history of one or more attacks of dysentery it should be remembered that this complication does occur in a very considerable number of individuals who have never suffered from dysentery or even from severe attacks of diarrhea Thus Futcher (1903) obtained no history of dysentery in 5 of 27 cases of liver abscess he observed Elliott (1915) was able to obtain a history of dysentery in only 47 of 116 cases Biggam and Ghalioungui (1933) in only 12 of 48 cases and Ochsner and Debakey (1935) in 52 cases observed by them obtained a history of previous diarrhea of dysentery in but 10 cases or o per cent and in an analysis of the literature of amebic abscess of the liver covering 318 cases they found that no less than 131 or 41 1 per cent gave no history of previous diarrhea. The writer has observed many cases of amebic abscess of the liver in carriers without any symptoms of diarrhea or dysentery and it is evident from reliable statistics that this complication frequently occurs in the absence of such a history

Location and Number of Abscesses — The most frequent location of amebic abscess of the liver is in the right lobe of that organ near the dome but abscesses may be located anywhere in the liver Clark (1925) in his analysis of 95 cases of liver abscess observed at autopsy found 53 or 55 7 per cent in the right lobe of the liver 16 or 16 8 per cent in the right and left lobes 15 or 15 7 per cent in all lobes and 8 or 8 4 per cent in the left lobe The writer has found that the majority of abscesses of the liver caused by *Endamœba histolytica* are located in the right lobe but in no less than 12 of 24 cases observed at autopsy they were not confined to this lobe although the oldest abscesses were found to be located in the right lobe

The number of abscesses present in the liver varies from one to many and the old idea that amebic abscess of this organ usually is a solitary abscess should be abandoned Thus Futcher (1903) found a single abscess in only 10 of 18 cases Strong (1925) in 13 of 23 cases Clark (1925) in 40 of 95 cases and the writer (1934) in only 9 of 24 cases observed at autopsy These data prove that multiple abscesses of the liver in amebiasis occur even more frequently than single abscesses a fact of great surgical importance

Pathology — *Macroscopically* the liver usually is found to be enlarged and areas of fatty degeneration may be present The abscess if large may be visible externally but small abscesses are frequently situated deep within the

Abscess of the Liver

The most frequent and important of the complications of amebiasis is the characteristic form of liver abscess which may follow the invasion of the liver by this parasite

Incidence — The incidence of amebic abscess of the liver apparently varies greatly in different localities and it is doubtless true that it occurs much more frequently in the tropics than in temperate regions Kartulis (1887) found that in 500 cases of dysentery coming to autopsy in Egypt no less than 55 per cent were complicated by liver abscess Strong and Musgrave, in the Philippines found liver abscess present in 23 per cent of 100 cases of amebic dysentery observed at autopsy while Clark in Panama found this condition in 95 of 186 cases of amebiasis or 51 per cent observed at autopsy In 78 fatal cases of amebic dysentery autopsied by the writer amebic abscess of the liver was found in 33 per cent of the cases

The data given above are those collected at the autopsy table and do not give a true picture of the incidence of this complication, for if the total number of cases of amebiasis occurring in any region be considered and not the fatal infections only in many of which the liver abscess has been the cause of death, it will be found that the incidence is very much lower Thus in 1 429 cases of amebic dysentery reported by Councilman and LaFleur (1891), including fatal cases, 21 per cent were complicated by abscess of the liver, while Tao (1931) observed this complication in 18 of 1000 cases of amebiasis, or 1 8 per cent The writer in 745 cases of amebic dysentery observed amebic abscess of the liver in approximately 5 per cent of the cases While this complication is frequently overlooked it must be admitted, if one considers the very large number of infections with *Endamaba histolytica* and the relative infrequency of amebic abscess of the liver especially in temperate regions, that the incidence of this complication is low certainly not exceeding 5 per cent

Predisposing Causes — Sex and age have much to do with the occurrence of amebic abscess of the liver As regards sex it is well known that males suffer much more from this complication than females Strong (1925) states that the Indian statistics show a ratio of 7 males to 1 female, while Futcher (1903) in 27 cases of liver abscess found 24 cases in males and 3 in females The writer in 24 consecutive cases of liver abscess observed no case in a female As regards age amebic abscess of the liver is a complication occurring in adults very few cases being reported in individuals less than 15 years of age Thus Rogers (1930) in nearly 400 cases of amebic abscess of the liver observed in Calcutta found that 70 per cent occurred between the ages of 21 to 40 years, 5 per cent after 50 years of age, and only 5 per cent below 20 years of age In only 2 cases did he observe an amebic abscess of the liver in children less than 10

of *Endamæba histolytica* There is no definite abscess wall but in slightly older abscesses there is a wall composed of connective tissue infiltrated with leukocytes and trophozoites of the ameba which are invading the surrounding tissue and enclosing a large mass of necrotic material similar to that observed in the younger abscesses In the large, old abscesses the following appearances are noted from within outward a zone of necrotic material of the composition already described a zone of connective tissue, the inner edge of which is necrotic but which becomes denser in structure peripherally a zone in which there is active proliferation of connective tissue cells and most externally a zone of dense connective tissue infiltrated with connective tissue cells The trophozoites of *Endamæba histolytica* occur usually near the border of the connective tissue zone in the necrotic areas and can not be found in the dense connective tissue of the wall of the older abscesses They are found most frequently in the medium sized abscesses and in the very earliest abscesses, indicated by the necrotic areas having no definite abscess wall which have been described The parasite reaches the liver from the intestine through the portal vein in the vast majority of cases but it may reach the liver through the lymphatics or the peritoneal cavity

Symptoms of Liver Abscess —The symptoms of liver abscess vary greatly in different individuals An abscess may develop to a considerable size with so few symptoms as not to attract the attention of the patient or physician but usually there are well marked symptoms which herald the beginning of abscess formation and which should always be looked for in every case of amebiasis as the early recognition of abscess formation enables one to prevent further development if proper treatment is instituted

Many years ago Rogers called attention to the symptoms which are present during invasion of the liver by *Endamæba histolytica* which he has called the presuppurative stage , and which the writer has observed in numerous instances Rogers (1935) in his latest description of this stage divides it into an acute and chronic form

In the acute form there is high fever a leukocytosis and an enlarged and tender liver while in the chronic form there is less fever less enlargement and tenderness of the liver and less leukocytosis In the acute form the temperature is remittent the decline being followed by profuse perspiration while in the chronic form the fever does not go as high and there is less sweating when it declines The leukocytosis in the acute form averages about 20,000 leukocytes per cu mm in the chronic form it is less The neutrophilic leukocytes are increased in the acute form and are not increased in the chronic form The duration of this presuppurative stage varies from two weeks to over one month The writer believes that the occurrence of daily fever accompanied by sweating tenderness over the liver and a leukocytosis in an individual infected with

organ. In such cases, unless the organ is sectioned, the abscesses may be overlooked. Adhesions of the liver to surrounding structures may be present, and the abscesses vary greatly in size from the large, solitary abscess generally located in the right lobe and sometimes occupying most of that lobe, to small abscesses a few millimeters in diameter. In cases of multiple abscess formation the abscesses vary in size and large and small abscesses may be scattered throughout the organ or be limited to one lobe, usually the right lobe. Besides the abscesses there may occur in the liver small areas of necrosis without any definite abscess wall which are the earliest stage of abscess formation.

The contents of amebic liver abscesses, in cases uncomplicated by secondary bacterial infection, are characteristic, consisting of a thick, semi-fluid, brownish red or chocolate colored material, which microscopically is seen to be composed of shreds of necrotic liver tissue, degenerated liver cells, leukocytes, blood and containing motile trophozoites of *Endamœba histolytica*. If there is a secondary bacterial infection, the abscess contents consist of the material mentioned together with pus and has a yellowish or yellowish green color. In uncomplicated amebic abscess of the liver the abscess contents are not pus but cytolysed liver tissue mixed with blood and are bacteriologically sterile.

In some patients dying of amebic dysentery there may be noted in the liver small, fibrous areas which have resulted from the healing of beginning abscesses. These areas indicate that the liver possesses great resistance to amebic infection and that spontaneous healing may occur even after beginning abscess formation.

The *abscess wall* in abscesses due to *Endamœba histolytica* is characteristic and varies in appearance with the age of the abscess. In the small, early abscesses the wall is not well differentiated, but in the medium sized and large abscesses the wall is seen as composed of more or less dense fibrous tissue lined internally with shreds of necrotic liver tissue giving it a shaggy appearance. If these abscesses be carefully washed out under running water, it will be found that strands of still intact connective tissue bridge the abscess cavity and between them is found the peculiar chocolate colored material consisting of blood, necrosed and cytolysed liver tissue and degenerated leukocytes and connective tissue cells. In the oldest abscesses the wall is thicker and is apt to be smooth internally or presents a slightly rough appearance. In the writer's experience in from 40 to 50 per cent. of amebic liver abscesses there is a secondary infection with bacteria, and when this occurs, the abscess wall is like that of a pyogenic abscess and the contents are largely pus mixed with some of the characteristic material present in a pure amebic liver abscess.

Microscopically sections through one of the youngest abscesses show an area of capillary congestion enclosing a mass of cytolysed liver tissue cells, red blood corpuscles, a few leukocytes, connective tissue cells and trophozoites

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Endamoeba histolytica almost invariably indicates invasion of the liver with a resulting hepatitis and that, while abscess formation may have already begun in some of these cases it is usually indicative of beginning abscess formation and prompt recognition and proper treatment will prevent further development of the condition

The symptoms produced by a liver abscess are somewhat variable in different individuals but usually consist of pain and tenderness over the liver, a daily fever accompanied by sweating during remissions and a marked leukocytosis with a relative increase in the neutrophilic leukocytes The pain is sometimes referred to the shoulder or the arm pit but usually is in the hepatic region and there may be marked tenderness in this region upon pressure At first the pain is aching in character and comes on gradually but becomes piercing or stabbing as the condition progresses It may come on very suddenly and when this occurs one should always think of a possible rupture of an abscess which has been latent in development

The fever is remittent at first but may become continuous or septic in type in rare cases there may be no fever during the development of the abscess, although this is very rare The temperature usually ranges between 38–39° C (100–102° F) with morning remissions to normal or below, accompanied by more or less perspiration If secondary bacterial infection be present, the fever may be much higher and the curve of a typical septic type

The leukocytosis in amebic liver abscess is very variable, and it should be remembered that a high leukocytosis does not always mean abscess formation, for a leukocytosis of 30 000 per cu mm may be present in an amebic hepatitis without abscess formation However if there is marked pain and fever, a high leukocytosis speaks in favor of abscess formation Elliott (1915) in 116 cases found that the average leukocyte count was 18 000 per cu mm, while in the writer's experience the count has varied from day to day in the same individual, an average count of from 15 000 to 20 000 leukocytes per cu mm being observed In those cases having a secondary bacterial infection the leukocyte count is consistently higher and in the writer's experience a count above 30,000 per cu mm almost invariably indicates the presence of secondary bacterial abscesses in the liver The relative leukocyte count in amebic abscess of the liver shows an increase in the neutrophilic leukocytes with a slight increase in the eosinophiles in some infections

Among other symptoms which are often present in amebic liver abscess, are nausea and vomiting headache chills emaciation and marked prostration The skin is of a sallow slightly jaundiced appearance and the patient has an apathetic, wearied expression and often presents the typical septic facies The pulse is rapid and weak if the condition has lasted for some time, and arrhythmias are observed frequently

TABLE III

Location of Rupture of Amebic Abscess of the Liver

Observer Reporting	No of Cases	Cases of Rupture	Pleura	Lung	Pericardium	Colon	Stomach	Duodenum	Bile Ducts	Vena Cava	Kidney	Lumbar Region
Cambay	10	3	2	1								
Craig	28	9	6	1	2							
Dutroulau	66	25	10	7	2	1	1					4
Elliott	116	7		7								
Futcher	27	20	5	9				1		3	1	1
Hoppel	25	6	2		4							
Howard	6	5			5							
Rouis	162	54	17	14	11	3	6		2			1
Waring	400	68	28	15	14	2	1		1	3	2	2
Total	740	197	70	54	38	6	8	1	3	6	3	8

The physical signs of abscess of the liver vary with the size and number of the abscesses There may be bulging of the chest wall over the site of the abscess, and there is always soreness or tenderness over the hepatic region Respiratory movements may be restricted on the affected side, and there may be rigidity of the abdominal muscles over the lower portion of the hepatic region The liver upon percussion usually shows an increase in the area of dullness and in those cases in which the abscess is large and situated in the upper portion of the right lobe the area of dullness is higher than normal in the axillary line and may extend posteriorly as high as the scapula and anteriorly to the nipple line If abscesses are present in the lower portion of the liver the area of dullness may extend well down toward the crest of the ilium Auscultation often shows nothing abnormal but there may be friction rubs or rales if the abscess has involved the pleura or the lung

Rupture of Liver Abscess — Owing to the fact that amebic abscess of the liver frequently is undiagnosed especially in temperate climates, rupture of the abscess is a not infrequent accident The accompanying table (Table III) gives the location of

the rupture in 740 cases of amebic liver abscess and is of interest from a surgical standpoint

From Table III it will be noted that in no less than 197 of 740 cases of amebic abscess of the liver, or 26 6 per cent, rupture occurred, thus demonstrating how frequently this condition is overlooked by the clinician

Abscess of the Lung

Endamoeba histolytica may reach the lung from the intestine through the blood stream and produce an abscess, or an abscess may be produced through the rupture of an amebic abscess of the liver directly into the lung The latter origin of amebic abscesses of the lung is the most frequent, the former being very rarely encountered

The incidence of lung abscess is small compared with liver abscess, the experience of most authorities showing that it does not occur in more than a very small fraction of one per cent of cases of amebiasis, and a primary abscess of the lung caused by this parasite is so rare as to be a medical curiosity On the other hand, *empyema* is a frequent complication of amebic abscess of the liver, owing to the rupture of such an abscess into the pleural cavity If there is no secondary bacterial infection, the exudate in the empyema is similar to that observed in an uncomplicated amebic liver abscess, but frequently, by the time that the liver abscess has ruptured, secondary bacterial infection is present, and the pleural cavity contains pus Empyema caused by a ruptured liver abscess frequently is overlooked being discovered at autopsy, or the empyema is not thought to be due to the ameba but to some bacterial infection.

Pathology — Macroscopically the diaphragm is often found adherent to the lung and the abscess cavity usually is continuous with that of the liver abscess if a rupture of such an abscess into the lung has occurred The location of such an abscess is always in the right lower lobe of the lung, but if the abscess is a primary one it may be located in any lobe but usually in the right lower lobe The contents of a lung abscess due to the ameba is similar to the contents of an amebic abscess of the liver, but if secondary bacterial infection is present the material may consist largely of pus The contents of a primary amebic abscess of the lung is more or less blood stained and consists of necrotic and cytolysed tissue with few or no pus cells unless secondary bacterial infection is present

Microscopically the abscess wall from within outwards consists of a zone of necrotic material a zone of connective tissue cells and lastly a zone of well organized connective tissue The abscess contents the inner wall of the abscess and the zone of connective tissue cells may show trophozoites of *Endamaba histolytica*

Amebic abscesses of the lung are almost invariably single abscesses and of comparatively small size The largest the writer has observed was about the size of an orange but larger lung abscesses have been described If secondary bacterial infection be present, numerous metastatic abscesses may be present in the lung

Symptomatology — The symptoms of a primary amebic abscess of the lung are similar to those of abscess of the liver, the invasion of the lung being accompanied by fever chills and more or less pain A cough develops with the expectoration of large amounts of the grumous chocolate or blood stained material from the abscess cavity in which trophozoites of *Endamœba histolytica* may be present The *physical signs* are dullness on percussion over the area in the lung occupied by the abscess lessened breath sounds and numerous coarse râles, while the patient rapidly loses weight becomes anemic and the general appearance is that of a case of pulmonary tuberculosis and this is the diagnosis that is frequently made in these cases

The symptoms of lung abscess when it follows the rupture of a liver abscess into the lung are those of liver abscess to which are added the symptoms described above Rupture of the liver abscess into the lung is sometimes accompanied by the very sudden development of a paroxysmal cough and severe pain in the chest while pleurisy and empyema are not infrequently noted in such cases the liver abscess having perforated into the pleural cavity as well as into the lung In some cases the development of an amebic abscess of the lung is insidious the first intimation that the patient has of the condition being the expectoration of brownish yellow sputum containing trophozoites of *Endamœba histolytica*

Amebic Abscess of the Brain

This is a very rare complication of amebiasis the incidence of infection being variously stated but only about 52 could be collected by the writer in the literature If one takes into consideration the hundreds of thousands of cases of amebiasis throughout the world it is evident that abscess of the brain must be a vary rare complication

Pathology — Brain abscesses due to *Endamœba histolytica* have almost invariably been single abscesses and the location has varied greatly The *parasite reaches the brain from the intestine through the blood stream and* produces cytolysis and destruction of tissue so rapidly that the duration of such abscesses seldom exceeds 2 weeks and death usually occurs in from 5 to 10 days

Macroscopically the abscess is surrounded by an edematous slightly congested area, and the abscess wall is thin or practically absent The contents

consist of blood stained, cytolysed and necrotic brain tissue, and, if a secondary bacterial infection is present, greenish yellow pus may fill the abscess cavity

Microscopically there is congestion of the vessels of the pia mater and infiltration of the tissue surrounding the abscess with a small number of leukocytes Sections through the invaded tissue of the brain show cytolysis of the tissue, degenerated nerve cells, lymphoid cells and trophozoites of *Endamaba histolytica* in the tissue forming the inner surface of the abscess cavity In many of the brain abscesses reported there has been evidence of a secondary bacterial invasion as shown by the presence of numerous pus cells in the abscess contents and in such cases the duration of the abscess has been shorter than in the uncomplicated infections

The symptoms of an amebic abscess of the brain are not characteristic but are those of brain abscess due to other causes The character of the symptoms varies with the location of the abscess and in the reported cases the abscess has almost invariably been located in the cerebrum Severe headache, vomiting, convulsions, delirium, hallucinations, various localizing symptoms and an absence of fever have been the symptoms most often observed In a pure amebic abscess of the liver meningitis apparently does not occur, and even when a secondary bacterial infection is present, it has rarely been observed

Abscesses of other organs, as the spleen, kidney, ovaries, pancreas and testicle have been reported but are excessively rare and of no general interest

Amebiasis of the Skin

Invasion of the skin by *Endamœba histolytica* has been reported by several observers and Engman and Meleney (1931) have reviewed the reported cases of such invasion dividing them into four classes i e those following drainage of an amebic abscess of the liver those following the drainage of the appendix or the large intestine those involving the skin in the region of the anus in cases of amebic colitis or dysentery those without any direct connection with the viscera Their description of the pathology of amebiasis of the skin demonstrates that there is the same cytolysis of tissue with the absence of inflammatory reactions which are characteristic of the pathology of amebiasis of the intestine and the liver and that it is only when a secondary bacterial infection is present that one observes the usual evidences of inflammation with pus formation

The symptoms of amebiasis of the skin are pain and tenderness in the invaded areas with edema and ulceration The ulcers are characterized by an irregular margin overhanging edges and a floor covered with granulation tissue The trophozoites of *Endamaba histolytica* may be demonstrated in the cytolysed tissue, and pus may be present due to secondary bacterial infection If ulcera

tion is not present as in cases where the parasite has invaded the edges of an operation wound, the edges of the wound become edematous, dusky red in color and areas of necrosis appear in which trophozoites may be demonstrated. The general symptoms may be fever, slight chills headache and local pain and distress. Amebiasis of the skin usually is a complication following operative procedures for the relief of amebiasis of some organ as the liver but primary invasion of the skin from the intestine through the blood stream has been reported, and the ameba has been demonstrated as the cause of the lesion

Amebiasis of the Appendix

Amebic appendicitis probably occurs much more frequently than is suspected, and the writer has no hesitation in stating that appendicitis caused by *Endamœba histolytica* is by no means a rare complication of intestinal amebiasis. In many carriers of this parasite symptoms frequently are present simulating those of a chronic appendicitis and it is probable that in many cases there is an actual invasion of the appendix by the ameba and that the symptoms are due to lesions which it has produced

That the incidence of this complication is considerable has been shown by Clark (1925) who found ulcerations in the appendix at autopsy in no less than 76 of 186 fatal cases of amebic dysentery and in the writer s (1934) examination of 60 fatal cases observed with reference to this complication amebic ulceration of the appendix was found in 16 cases or 26 6 per cent

The pathology of amebic appendicitis both macroscopically and microscopically is similar to that of amebic dysentery The appendix usually is tumefied and the ulcers while small have the same structure as those occurring in the intestine while the microscopical pathology is similar to that of amebic invasion of the intestine already described Trophozoites of *Endamœba histolytica* may be observed in any of the coats of the appendix but are most numerous in the mucous and submucous coat Perforation of the appendix by an amebic ulcer has been reported repeatedly and is probably more frequent than is generally believed

The symptomatology of appendicitis due to this parasite generally is that of a subacute or chronic appendicitis the symptom being recurrent attacks of dull pain accompanied by soreness in the appendicular region lasting for hours or days with little or no fever and only a very slight leukocytosis These attacks may recur for weeks or months and may subside spontaneously or be followed by more acute symptoms or even by perforation of the appendix In some cases the attack may almost exactly simulate that of an acute appendicitis from bacterial infection there being a sudden onset severe pain over the appendix and a high temperature In such cases there may be a marked

leukocytosis, and the entire picture is that of an acute appendicitis, while the physical signs are typical of that condition In the more common or chronic form of the infection the physical signs are tenderness over the appendix with slight rigidity of the muscles during the attacks, while in the intervals there may be no tenderness or rigidity

Perforation of the Intestine

Perforation of an amebic ulcer of the intestine, while a frequent cause of death in amebic dysentery, is not a common complication, the writer in 100 consecutive autopsies upon cases of amebic dysentery observing it in but four cases Perforation may occur in any portion of the large intestine and is usually followed by a general peritonitis, although, if adhesions are present, a pericolic or pericecal abscess may result

Peritonitis

Aside from the general peritonitis which usually follows the perforation of an amebic ulcer many cases of chronic amebic dysentery or diarrhea present a local peritonitis, often accompanied by numerous adhesions, if repeated attacks of dysentery have occurred At autopsy in old chronic cases of amebic dysentery areas of local peritonitis are often observed covered with fibrin and lymph and with newly formed adhesions uniting the intestine to the surrounding organs or to the coils of the small intestine A liver abscess may rupture into the abdominal cavity causing a general or localized peritonitis, or a local peritonitis may result from extension of inflammation from a liver abscess without rupture into the peritoneal cavity

Intestinal Hemorrhage

While all cases of amebic dysentery are characterized by more or less blood in the stools a severe intestinal hemorrhage is comparatively rare in amebiasis even when ulceration may be very extensive Deaths have been reported from intestinal hemorrhage in acute and chronic amebic dysentery, but the writer has never observed such a case although he has observed several instances of severe hemorrhage during the course of an infection It is indeed surprising that severe and fatal hemorrhages are not more frequently observed when one considers the number size and penetration of the ulcers in severe amebic dysentery, but it is a fact that this complication is a rare one In the fulminant cases of amebic dysentery fortunately rare hemorrhage is much more often severe and contributes greatly to a fatal result

Urinary Amebiasis

Several authorities have reported invasion of the bladder by *Endamœba histolytica* with the presence of trophozoites in the urine Most of these reports are open to question although it is true that in very rare instances such an invasion has occurred The writer has observed but one case and in this a fistula had been established between an ulcer in the intestine and the urinary bladder with consequent invasion of the wall of the bladder and the appearance of trophozoites in the urine

Invasion of the Gall Bladder

The invasion of the gall bladder by *Endamœba histolytica* has been reported by several writers notably by Smithies (1928) while the writer observed a case reported by Nichols (1922) in which the enlarged gall bladder contained purulent material in which active trophozoites were found and sections of the organ showed trophozoites in the thickened wall The writer believes that very rarely this parasite invades the gall bladder but that it is not a frequent cause of cholecystitis as claimed by some observers

Amebic Granulomata

Rarely and usually in long continued amebic infection of the intestine granulomatous masses may be found especially in the rectum which may closely resemble carcinomata and have been mistaken for the latter Often these masses have an ulcerated surface and are hard and indurated and the amebae can be demonstrated in scraping from the ulcerated areas These chagomata as they are sometimes called in recent literature are important because of the liability of confusing them with malignant disease and also because they may cause serious obstruction of the intestine They are sometimes polypoid in appearance or consist simply of hard masses of fibrous connective tissue They can only be distinguished from malignant tumors by a microscopic examination of sections Hu (1937) reported 5 cases of papillomatous lesions in the anal region caused by *Endamœba histolytica* and Donald and Brown (1940) reported 2 cases of amebic granulomata of the rectum

SEQUELAE

Very little is known of possible sequelae following long continued latent infection with *Endamœba histolytica* but it is probable that in such infections the constant absorption of toxic material through the lesions which are present always even in unapparent infections may result in certain sequelae of importance

Following long continued amebic infection which has been manifested by symptoms of diarrhea or dysentery, a condition of chronic diarrhea often is present even after the amebic infection has been eliminated This condition is caused by the replacement of large areas of the mucous membrane of the large intestine by dense fibrous scar tissue following the healing of the ulcerative lesions produced by the infection In some of these individuals a normal stool seldom occurs while in others attacks of severe diarrhea follow the intake of large quantities of fluid In such cases the diarrhea is most pronounced in hot weather, when the intake of fluid is considerable, while normal or nearly normal stools may occur in cold weather This sequela of amebic infection is important, as it often leads to more or less invalidism while the recurrent attacks of diarrhea may be interpreted as either a new infection with *Endamaba histolytica* or as a relapse of an old infection which was thought to be eliminated Such cases have been treated often with emetine or other amebacidal drugs without any effect upon the diarrhea and with injury to the patient as such treatment is not indicated In all such cases a careful examination should be made for the parasite, and if it is not demonstrated the patient should be informed of the reason for the diarrhea

Sprue or psilosis often has been confused with chronic amebic infection, because of the chronic diarrhea which sometimes follows long continued amebic infection Some of these patients even develop a sore tongue, and the stools may be similar to those observed in sprue and in patients presenting these symptoms in addition to the diarrhea the differential diagnosis may be difficult

Other sequelae that follow long continued amebic infection are an enormous thickening of the connective tissue of the bowel and a constriction of its calibre, which rarely may lead to obstruction of the intestine The writer has observed at autopsy upon subjects dying of chronic amebic dysentery such an excessive thickening of the coats of the large intestine that it resembled a piece of rubber hose and in such cases of course a condition of chronic diarrhea was present, which undoubtedly contributed largely to the fatal issue

Diagnosis

The diagnosis of amebiasis must be established by the demonstration of *Endamœba histolytica* in the feces exudates or tissues of patients suspected of harboring this parasite Clinically there are no pathognomonic symptoms of amebiasis and while one may suspect the infection from the clinical picture which is presented it must be admitted that even the most typical symptoms of amebiasis may be simulated by other disease conditions and that even a diagnosis of acute amebic dysentery is really worthless unless the parasite is demonstrated in the stools of the patient It is thus evident that we must depend upon laboratory methods for a definite diagnosis but it is necessary to

consider the clinical differentiation of some of the most common conditions that may be confused with amebic infection even though the differential diagnosis must be confirmed by the absence of *Endamœba histolytica* It should be remembered that a large majority of infections with this parasite present symptoms which may occur in other disease conditions within the gastro intestinal tract and that in all such conditions the stools should be examined for this parasite

Bacillary Dysentery — This is probably the infection most apt to be confused with amebic dysentery and it is true that our statistics regarding the relative occurrence of bacillary and amebic dysentery prior to the World War I are almost worthless because of the frequent confusion of the two infections Many cases of bacillary dysentery resemble in their symptomatology cases of amebic dysentery and it is also true that both may co-exist thus further confusing the clinical picture Remembering that the symptoms of many cases of bacillary and amebic dysentery are indistinguishable there are some features in which the bacillary infections differ quite markedly from amebic infections in a certain proportion of infected individuals

The onset of bacillary dysentery is much more apt to be very sudden than is that of amebic dysentery, and prostration is more rapid and severe In bacillary dysentery fever is always present and more severe than in amebic dysentery while chills nausea vomiting and arthritic symptoms are present in bacillary dysentery and usually absent in amebic dysentery The character of the stools is essentially different in the two conditions and will be discussed later Relapses are the rule in amebic dysentery and the exception in bacillary dysentery while a fatal ending of the primary dysenteric attack is much more frequent in bacillary than in amebic dysentery Tenesmus is more marked in the bacillary forms of dysentery and there is greater generalized tenderness over the abdomen Fulminant cases of amebic dysentery may so closely simulate severe bacillary dysentery that a clinical differentiation is impossible and this is still more frequently true of the milder types of bacillary dysentery The vast majority of the cases of bacillary dysentery observed in the United States simulate clinically the amebic form and it is certain that many cases of amebic dysentery have been diagnosed as bacillary dysentery in this country owing to similarity of clinical symptoms and lack of laboratory confirmation of the diagnosis The following observations are of value in assisting in a clinical differentiation but the diagnosis of either form of dysentery should always be confirmed if possible by the demonstration of the parasite concerned

Amebic dysentery usually is a chronic endemic infection while bacillary dysentery is an acute epidemic infection the period of incubation in amebic dysentery is generally unknown while it usually is a week or less in the bacillary forms the onset in amebic dysentery usually is insidious or slow while in

bacillary dysentery it is acute the course in amebic dysentery is apt to be chronic with acute exacerbations while in bacillary dysentery usually it is acute subsiding or terminating fatally in a few days although it may become chronic liver abscess complicates amebic dysentery but does not occur in bacillary dysentery tenesmus usually is moderate in amebic dysentery but intense in the bacillary forms while death is infrequent in amebic dysentery during the initial attack it is much more frequent in bacillary dysentery

Balantidial Dysentery — Dysentery produced by the ciliate *Balantidium coli* can not be differentiated clinically from that produced by *Endamæba histolytica* and pathologically the two conditions are very similar

Schistosomal Dysenteries — Dysenteries produced by the flukes *Schistosoma mansoni* or *Schistosoma japonicum* are clinically similar to amebic dysentery so far as the symptoms of dysentery are concerned but other symptoms are present in infections with *S mansoni* which would serve to differentiate this form of dysentery There is a history of the occurrence of urticaria fever, abdominal pains dyspnea chills and anorexia before the appearance of dysentery caused by the migration and maturation of the worms while enlargement of the liver and spleen and the development of fistulous tracts extending into the structures surrounding the rectum with papillomatous masses in the rectum occurring after the dysenteric symptoms have lessened or ceased are prominent symptoms and signs In infections with *S japonicum* the differentiation from amebiasis and amebic dysentery is clinically impossible in most instances and laboratory methods must be employed in the diagnosis

Chronic Mucous Colitis — It is often difficult to differentiate amebic enteritis from chronic mucous colitis but the occurrence in the stools of the patient of the characteristic mucus casts of the bowel or long shreds of mucus in mucous colitis and the absence of much blood and tenesmus usually differentiates the two conditions In mucous colitis there is a history of recurrent attacks of severe abdominal colic, sometimes accompanied by nausea and vomiting followed by the passage of much mucus frequently in the form of strings or casts of the bowel. In addition there may be a diarrhea persisting for a day or more or constipation may be present The abdomen in mucous colitis usually is distended and tender during the acute attack and a slight fever may be present Chronic mucous colitis usually occurs in nervous individuals especially women who suffer from chronic spastic constipation between the attacks The symptoms noted usually are characteristic of chronic mucous colitis but in some infections with *Endamæba histolytica* similar symptoms may be present and in some cases there may be a combined infection with this ameba and a mucous colitis In every patient suffering from the latter condition a microscopical examination of the stools should be made for *Endamæba histolytica* for the elimination of infection with this parasite will result in improvement of the colitis

Chronic Ulcerative Colitis —While there is much discussion regarding the etiology of conditions diagnosed as chronic ulcerative colitis it is true that colitis accompanied by ulceration of the bowel not due to the dysentery bacilli or *Endamoeba histolytica* does occur and the symptoms of this condition so closely simulate those of amebic dysentery that a diagnosis usually is impossible without the aid of stool examinations In ulcerative colitis proctoscopic examinations are most valuable in differentiating it from amebic infection In ulcerative colitis the proctoscopic examination usually shows a much congested mucous membrane which bleeds easily and often is covered with a mucopurulent exudate Scattered upon this congested membrane may be seen either pin head superficial erosions or definite ulcers without undermined edges or any connection between the ulcers as in amebic dysentery In long standing cases there may be thickening of the intestinal coats and most of the mucous membrane may have been replaced by scar tissue In such cases a differential diagnosis between chronic amebic dysentery and ulcerative colitis is impossible unless *Endamoeba histolytica* is demonstrated in the stools or in material removed from the ulcers

Chronic Enteritis — It is impossible to differentiate clinically enteritis from one caused by *Endamoeba histolytica* and resort must be had to a microscopical examination of the stool or to other laboratory methods

It is unnecessary here to discuss the many other conditions that may be confused with amebiasis as helminth infections malarial dysentery tuberculosis of the bowel kala azar hemorrhoids and malignant disease of the intestine or rectum and syphilis All of these conditions may be differentiated by well known laboratory or clinical methods but it should always be borne in mind that any one of them may be complicated by an amebic infection

Diagnosis of Amebic Abscess of the Liver —The occurrence of a daily fever accompanied by tenderness or pain over the hepatic region and a slight leukocytosis in an individual showing *Endamoeba histolytica* in the stools usually indicates an amebic hepatitis and the existence of the pre suppurative stage of liver abscess as described by Rogers (1935) The actual development of an abscess is evidenced by marked tenderness over the hepatic region severe pain in that region a daily fever which remits in the early morning hours accompanied by sweating and a marked leukocytosis Anorexia or diminished appetite gastric disturbances insomnia and loss of weight are also noted while the physical signs vary with the location of the abscess As the most frequent site of an amebic abscess of the liver is in the upper portion of the right upper lobe upward enlargement of this lobe is detected upon percussion while the Roentgen ray will show a dome shaped shadow the highest portion of the shadow being over the upper boundary of the right lobe of the liver There is always some enlargement of the hepatic area wherever the abscess may be located and frequently there is edema and bulging in some portion of this

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method of diagnosis is ascertained Vallarino (1925) states that the Roentgen graphs clearly show defects which are characteristic of amebiasis consisting of a mottling of the affected portions of the intestine, the lesions being most frequently noted in the cecum and ascending colon while Ikeda (1934) states that the findings vary with the stage of the infection the extent and activity of the lesions and that no characteristic changes are noted in the early stage of intestinal amebiasis Later fine saw tooth like projections are noted along the wall of the colon and still later fine feathery or thorny filling defects In the subacute and chronic stages of amebic dysentery he noted a shortening or contraction of the intestinal wall with induration and filling defects As stated by Ikeda the roentgenologic findings are not diagnostic but are very suggestive and certainly indicate the location and degree of involvement in this condition and in this way are most valuable in demonstrating active lesions

There is no question however of the great value of Roentgen ray examinations in the diagnosis of amebic abscess of the liver Young and Bristow (1937) in the examination of 25 cases obtained a positive diagnosis by this means in all and Ochsner and DeBakey obtained a positive diagnosis in 132 of 150 cases of amebic liver abscess or 88 per cent in which roentgenography was employed for this purpose In all suspected cases roentgenography should be used even though the stools may be negative for *Endamœba histolytica* for amebic abscess of the liver frequently occurs after the primary intestinal infection has disappeared or has been eliminated by treatment

Amebic Hepatitis — The diagnosis of an acute or chronic amebic hepatitis is most important as prompt treatment may save the patient from the development of a liver abscess In all cases of liver abscess caused by this parasite there is a preliminary stage in which symptoms of a hepatitis may be recognized while in some cases a form of chronic hepatitis develops due to repeated invasion of the liver by *Endamœba histolytica* but in which the resistance of the patient has prevented actual abscess formation In the acute hepatitis preceding abscess formation the symptoms are more or less pain over the liver fever and the other symptoms characteristic of inflammation of that organ accompanied by a leucocytosis while in the chronic form of amebic hepatitis the patient usually is underweight has frequent so-called bilious attacks during which nausea and vomiting of bile stained fluid anorexia constipation or diarrhea are present together with slight fever at times and a sense of discomfort or aching over the hepatic region with more or less tenderness upon pressure Treatment with emetine usually will cause prompt disappearance of these symptoms if they are due to *Endamœba histolytica* while it will have no effect if the hepatitis is due to some other cause In all patients giving a history of previous attack of amebiasis and presenting the symptoms of a chronic hepatitis a most careful examination of the stools should be made for *Endamœba histolytica*

area over the location of the abscess The general appearance of patients having liver abscess is cachetic there being some degree of anemia present, while the skin may be slightly jaundiced and emaciation may be marked

A differential diagnosis between amebic liver abscess and other conditions affecting the liver is most difficult and one has to consider very carefully the history the symptomatology and physical signs and use all laboratory methods that are available in the diagnosis of the various infections and disease conditions that may be present in the liver remembering that the mere presence of *Endamœba histolytica* in the stools of the patient does not prove that the condition present in the liver is an amebic abscess as intestinal amebiasis may exist as a complication only It is very evident from the number of cases of amebic abscess of the liver first diagnosed upon the autopsy table, that the recognition clinically of this condition is difficult and that it is frequently overlooked or wrongly diagnosed It should also be remembered that amebic abscess of the liver frequently occurs in patients who have never suffered from diarrhea or dysentery and that the absence of such a history is no proof that the ameba has not invaded the liver A therapeutic test of much importance in the diagnosis of this condition is the administration of a few doses of emetine hydrochloride, which if followed by marked improvement in the symptoms, indicates that the condition present is caused by *Endamœba histolytica*

Diagnosis of Abscess of the Lung — The differential diagnosis of primary amebic abscesses of the lung is usually impossible without the demonstration of *Endamœba histolytica* in the sputum while in those cases in which an amebic abscess of the liver has ruptured into the lung the diagnosis usually is possible because of the sudden development of a paroxysmal cough accompanied by pain in the chest and the expectoration of the peculiar material like anchovy sauce characteristic of the contents of an amebic liver abscess However, one must demonstrate the ameba in the sputum before the diagnosis of amebic abscess of the lung can be accepted

Diagnosis of Amebic Abscess of the Brain — As brain abscesses due to *Endamœba histolytica* usually are secondary to a liver abscess, the history of such an abscess is of great service in the differential diagnosis of the brain abscess and unless such a history can be obtained or a liver abscess is present, it is impossible to differentiate an amebic abscess of the brain from abscesses in this organ due to other causes While the presence of intestinal amebiasis may be suggestive it should be remembered that this is a very common condition, while an amebic abscess of the brain is very rarely encountered

Roentgen Ray in Diagnosis — While some authorities, notably Vallarino (1925) Smithies (1926) and Ikeda (1934) have urged the value of the Roentgen ray in the differential diagnosis of intestinal amebiasis it is certainly true that much remains to be accomplished in this field before the exact value of this

method of diagnosis is ascertained Vallarino (1925) states that the Roentgenographs clearly show defects which are characteristic of amebiasis consisting of a mottling of the affected portions of the intestine the lesions being most frequently noted in the cecum and ascending colon while Ikeda (1934) states that the findings vary with the stage of the infection the extent and activity of the lesions and that no characteristic changes are noted in the early stage of intestinal amebiasis Later fine saw tooth like projections are noted along the wall of the colon and still later fine feathery or thorny filling defects In the subacute and chronic stages of amebic dysentery he noted a shortening or contraction of the intestinal wall with induration and filling defects As stated by Ikeda, the roentgenologic findings are not diagnostic but are very suggestive and certainly indicate the location and degree of involvement in this condition and in this way are most valuable in demonstrating active lesions

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Laboratory Diagnosis

The diagnosis of amebiasis should rest upon the demonstration of *Endamœba histolytica* in the feces exudates or tissues of suspected patients, and no diagnosis is of real scientific value unless this parasite has been demonstrated, or specific treatment has eliminated the symptoms that may be present with complete recovery of the patient and even the therapeutic test often is open to question Unfortunately the intestine of man harbors no less than four other species of ameba which are not pathogenic and which must be differentiated from *Endamœba histolytica* and such differentiation is impossible, unless the person making the microscopical examinations has had considerable experience and been well trained in the differentiation of these organisms

In the diagnosis of amebiasis the laboratory methods available are the examination of the feces employing either unstained or stained smears, the cultivation of the parasite the complement fixation test and the examination of stained tissue sections Many methods of staining and cultivation have been devised, but only the most useful will be considered here, while the reader is referred to the work of the writer The Etiology, Diagnosis and Treatment of Amebiasis' (1944) for a more extended discussion of laboratory procedures

Examination of the Feces — Perhaps the most important fact to bear in mind in the examination of the feces for *Endamœba histolytica* is the very great importance of repeated examinations if preceding ones have proven negative for this parasite A single examination of an unstained preparation of the feces will fail to show the parasite in over 60 per cent of the positive cases, unless a saline purgative is given previous to the examination, except in acute diarrheal or dysentery cases when the examination usually is positive Even when all available methods of stool examination are employed, a few positive cases will escape detection, unless symptoms of intestinal irritation be present and Sawitz and Faust (1942) found that the examination of a single preparation stained with hematoxylin or iodine proved unsuccessful in demonstrating the ameba in less than one in five known infections that even using concentration methods only about one out of three or four infections were detected in a single examination and that five examinations resulted in the demonstration of the ameba in from 70 to 90 per cent of the cases examined Thus it is evident that repeated examinations of the feces often must be made even when the best available methods are employed, and that one should never rest content with a negative result in a single examination of the feces

In the examination of the feces it is most important that freshly passed specimens be examined if possible for while the cysts of *Endamœba histolytica* may be demonstrated in stools for many hours after passage it is essential that for the demonstration of the motile trophozoites freshly passed stools be examined,

if the best results are to be obtained It is always best even if formed stools are to be examined for the cysts that the specimen be examined as soon after passage as possible especially if staining methods be employed The container receiving the feces should be free from any antiseptic solution and if any form of oil barium or bismuth has been used by the patient he should be cautioned to suspend the administration for a few days before having the stool examined for the ameba It is also wise to examine the whole stool for evidence of the presence of mucus or blood as small specimens frequently do not show these even though present It should also be remembered that if one desires to demonstrate the motile trophozoites, the stool must be of fluid or semi fluid consistence while if the cysts are to be searched for the stool should be formed or semi formed Thus it is necessary, if the stool is not fluid to administer a saline cathartic if one desires to demonstrate the trophozoites and for this purpose magnesium sulphate is excellent

It has been shown conclusively that a larger percentage of positive examinations are obtained after a saline cathartic than if the formed stool be examined The feces may be examined in unstained smear preparations and in stained smears either by the iodine method or stained with hematoxylin In examining for the motile trophozoites unstained smears should always be employed and usually it is possible to make a diagnosis of *Endamaba histolytica* in such smears if properly prepared while in the examination of the formed stool for the cysts the iodine stained preparation is necessary

Unstained Smear Preparations — If the fluid feces contain flakes of blood stained mucus a minute amount of such material is placed upon a microscopic slide covered gently with a cover glass and examined at once using ocular 10 x objective 1 mm If the stool does not contain blood stained material a capillary drop of normal saline should be placed upon a microscopic slide and a minute portion of the stool should be thoroughly mixed in it and covered with a cover glass care being taken that the preparation is not too thick If newspaper print can be read through the preparation it will be found suitable for examination After picking up the organisms with the low power ocular and objective they should then be studied with the high power (4 mm) objective If the stool is formed a small portion is thoroughly mixed with normal saline upon a microscopic slide and covered with a cover glass while a second preparation should be made upon the one slide At least three preparations of the feces should be examined before a negative report is returned

Iodine Preparations — In examinations for the demonstration of the cysts of *Endamæba histolytica* and their differentiation from those of the other species living in the intestine of man iodine preparations are essential The iodine preparations should be examined along with unstained preparations but it should be remembered that the iodine solution should never be used in examina

tions of the motile trophozoites but only for the cysts The iodine solution used has the following formula

Iodine	7 grams
Potassium iodide	4 grams
Distilled water	100 c c.

The potassium iodide is dissolved in the distilled water, and the iodine is then added A saturated solution of iodine in a 5 per cent aqueous potassium iodide solution gives similar results

A drop of the iodine solution is placed upon a microscopic slide, and a small amount of feces mixed with it and covered with a cover glass The preparation should be allowed to stand for at least 5 minutes before examination so as to allow penetration of the cysts by the iodine With this solution it is possible to count the nuclei in the cysts and to distinguish their structure while glycogen vacuoles if present stain a dark brown With the iodine stain it is possible to differentiate the cysts of *Endamœba histolytica* from the cysts of other species of ameba or from flagellates and thus this method is of the greatest value in the diagnosis of amebiasis

Concentration Methods — Several methods of concentrating the cysts of *Endamœba histolytica* have been devised and are most useful in the diagnosis of this organism The most efficient is that of Faust and his colleagues (1938), which is as follows

1 Thoroughly mix one part of the formed stool, about the size of a pea, with about 10 parts of lukewarm water in a clean glass container

2 Strain 10 c c of this mixture through one layer of wet cheese cloth, previously placed in a small funnel into a Wassermann tube

3 The filtrate in the tube then is centrifugalized for 45 to 60 seconds at the top speed of an International clinical centrifuge about 2,500 revolutions per minute The supernatant fluid is poured off 2 or 3 c c of distilled water added the tube thoroughly shaken to distribute the sediment, and additional water added The tube then is centrifugalized as before, and the process is repeated until the supernatant fluid is clear

4 After the last centrifugalization the clear supernatant fluid is poured off, and 3 to 4 c c of a 33 per cent zinc sulfate solution, which should have a specific gravity of 1 180 are added The sediment is mixed thoroughly with this solution, and enough of the zinc sulfate solution is added to fill the tube to within one half inch of the rim

5 The tube then is centrifugalized for at least 90 seconds at top speed, then preparations are made from the material floating upon the surface by placing several platinum loopfuls upon a microscopic slide, adding a drop of iodine solution and mixing

The microscopic examination of such material has resulted in demonstrating the cysts of *Endamoeba histolytica* when other methods have failed and it is also most valuable in the examination of the feces for the ova of helminths. When one is experienced in the technique it consumes little time and it should be employed in all cases in which ordinary methods of stool examination have proven negative for the ameba. This is essentially a concentration and flotation method and is a great step in advance in the diagnosis of amebiasis.

Stained Preparations. — The employment of hematoxylin stained preparations of the feces usually is not necessary in the diagnosis of amebiasis but in some instances where repeated stool examinations by ordinary methods have proven negative stained preparations will give positive results. The use of any staining method requires experience and technical ability, is time consuming, usually unnecessary and should not be employed as routine procedures for these reasons. When it is desired to study the minute morphology of amebae or where it is necessary to send fluid or semi fluid material by mail for diagnosis, it is essential that stained preparations be employed. In the latter case the feces should be smeared upon microscopic slides and immediately fixed with sublimate solution, placed in a mailing tube filled with 70 per cent alcohol and mailed to the laboratory where they may be stained and examined.

The *fixation* of the specimen of stool is essential in any method of staining and the fixative usually employed is Schaudinn's fluid, consisting of a saturated solution of mercuric chloride in water 2 parts and absolute or 95 per cent alcohol 1 part. These are mixed and to each 100 c c there is added 5 c c of glacial acetic acid. The mixture should be slightly warmed just before it is used. It will keep indefinitely. In fixing the specimen proceed as follows: A small portion of blood stained mucus or fluid fecal material or of an emulsion of the feces if the stool be formed, is smeared rapidly upon a microscopic slide and immediately immersed in the warm Schaudinn's fixative, allowed to remain for at least 15 minutes, after which one of the hematoxylin stains is employed in staining. The smear must be prepared very rapidly and at once immersed in the fixing solution while still moist, for if drying occurs the preparations will be useless for staining owing to the changes in the morphology of the nucleus of *Endamoeba histolytica* and the other species caused by drying.

Many staining methods have been devised for *Endamoeba histolytica* but the writer has found the following the most generally useful.

Faust's Stain. — This method was recommended by Faust (1932) and will be found to give excellent results.

1. Fix in Schaudinn's fluid heated to a temperature of 60° F for 2 minutes.

2. Immerse smears in 70 per cent alcohol to which enough iodine has been added to give the mixture a port wine color, then 70 and 50 per cent alcohol, leaving in each 2 minutes.

3 Wash in running water for 2 minutes

4 Immerse smears in 2 per cent aqueous iron alum solution at 104° F for 2 minutes

5 Wash in running water for 3 minutes

6 Stain in a one half per cent aqueous hematoxylin solution for 2 minutes

7 Wash in water for 2 minutes

8 Differentiate in *cold* aqueous iron alum solution 2 per cent

9 Wash in running water for 10 to 15 minutes

10 Immerse smears successively for 2 minutes each in 70, 80, 90 per cent and absolute alcohol

11 Clear with xylol

12 Mount in xylol balsam

In employing this or any other stain in the diagnosis of *Endamœba histolytica* it should be remembered that *it is vitally important that at no stage of the staining process should the smears be allowed to dry for drying will destroy entirely the typical morphology of the organism* and render a differential diagnosis impossible

Many other methods of staining have been recommended by various authorities and for these the reader is referred to the writer s book entitled "The Laboratory Diagnosis of Protozoan Diseases"

Cultures in Diagnosis — The cultivation of *Endamœba histolytica* has made possible the use of cultural methods in the diagnosis of this organism and it is true that a larger percentage of positive results may be obtained with cultures than with the direct microscopical examination of the stools In the examination by St John and the writer (1927) of 71 individuals we found that using the cultural methods of examination 11 or 15 49 per cent were positive for *Endamœba histolytica* while only 6 or 8 45 per cent were positive by direct microscopical examination of the stools and in a recent series of examinations by Nauss and Salinger of 270 individuals by culture 9 or 8 3 per cent were positive while only 3 or 1 1 per cent were positive by direct smear examinations of the feces Many culture media have been devised for the cultivation of *Endamœba histolytica*, but for diagnostic work the more simple media are most suitable and the one that the writer would recommend for routine diagnosis is the Locke serum medium introduced by him in 1926 This medium is prepared as follows It consists of a mixture of a modified Locke solution and either inactivated human horse or rabbit blood serum preferably human blood serum The Locke solution has the following formula

Sodium chloride	9 00 gm
Calcium chloride	0 24 gm
Potassium chloride	0 42 gm
Sodium bicarbonate	0 20 gm
Distilled water	1,000 c c

This mixture is filtered and autoclaved at 15 pounds pressure for 15 minutes and then allowed to cool There is then added to it one part of inactivated blood serum to each 7 parts of the Locke solution After adding the blood serum the mixture is filtered through a Berkefeld filter until it comes through clear which may require two or even more filtrations After cooling the mixture is placed in test tubes about 10 c c in each tube and incubated at body temperature for 24 to 36 hours to determine sterility If found sterile the tubes should be kept in an incubator at 37° C (98 6° F) until used The reaction does not need adjusting The blood serum is inactivated by heating for one half an hour at 56° C (131° F) At the time the tubes are inoculated the best results will be obtained if a minute amount of rice flour be added to the inoculated tubes

Great care must be used in the inoculation of the tubes and experience is required in cultivating the organism before the best results are obtained As cultivation is a purely laboratory procedure the exact technique will not be described here and those interested are referred to the writer s work ' The Laboratory Diagnosis of Protozoan Diseases for descriptions of the various media and the technique of cultivation

Complement Fixation Test in Diagnosis — The writer in 1927 demonstrated that the blood serum of individuals infected with *Endamaba histolytica* contained complement fixing substances and later (1928 19 9 1930 1931 1933) described the technique of a complement fixation test and the results obtained with it in the diagnosis of amebiasis in man and animals Since his original observations numerous authorities have confirmed the existence of complement fixation in amebiasis and have published modifications of his complement fixation test for this infection Thus Spector (1932) Menendez (1932) Heathman and Sherwood (193) Tsuchiya (1934) and Weiss and Arnold (1934) all have demonstrated complement fixing bodies in the blood serum of individuals suffering from amebiasis and Tsuchiya and Weiss and Arnold have described modifications of the writer s complement fixation test for this condition

The complement fixation reaction using antigens prepared by extracting cultures of *Endamaba histolytica* apparently is specific for infection with this parasite and the complement fixation test is of very definite value in the diagnosis of amebiasis but should not replace the demonstration of the organism in the feces if facilities are available for such demonstration This test can only be made in serological laboratories by well trained serologists and for this reason is not available for use in the physician s clinical laboratory The results obtained with it are excellent and it is probable that in time it will become as generally useful as is the Wassermann test in syphilis

The writer (1934) has given the results obtained with his complement fixation test in 1 000 individuals in whom the results of the test were checked by a microscopical examination of the feces Of the 1 000 individuals tested

175 or 17 5 per cent gave a positive result with the test, and of these the stools were positive for *Endamaba histolytica* in 157 or 89 7 per cent Of the 18 individuals in whom the parasite was not found in the feces, 7 had sus picious intestinal symptoms, while in 11 the diagnosis of chronic ulcerative colitis had been made Of the 825 individuals giving a negative reaction with this test *Endamaba histolytica* was found in 12 or only 1 4 per cent, thus proving that while all individuals infected with this parasite do not give a positive reaction the percentage that do not is a very small one The infesta tion of the intestine with other species of ameba or other protozoan parasites does not cause a positive complement fixation reaction when the *Endamaba histolytica* antigen is employed nor do bacterial infections give such a reaction In the writer s experience this test does not give a positive reaction with other conditions than amebiasis and the disappearance of the positive reaction after treatment which has succeeded in eliminating the parasite, is positive proof of the specificity of this complement fixation test Where it is impossible to demonstrate the ameba in suspected cases of amebiasis, or where fecal examina tion by a trained observer can not be made, blood serum could be sent to labo- ratories making this test for diagnosis, and under such conditions it is of practical value in the diagnosis of amebiasis The test should also be useful in checking the effect of any form of treatment, for if the parasite is eliminated by the treat ment the positive complement fixation reaction will disappear within a few days or weeks usually within two to three weeks after the cessation of treatment

The Differential Diagnosis of Endamaba Histolytica from Other Amebae —If but one species of ameba occurred in the intestine of man and that species, *Endamaba histolytica* the diagnosis of amebiasis would be a comparatively simple matter but as no less than five species inhabit the human intestine the diagnosis is difficult owing to the necessity of differentiating these various species The most common species in the intestine of man is *Endamaba coli*, while next in order of frequency come *Endolimax nana*, *Endamaba histolytica*, *Iodamaba butschlii* and *Dientamœba fragilis* The greatest confusion in the differential diagnosis of *Endamœba histolytica* is caused by *Endamaba coli* and *Endolimax nana* the other species occurring much more infrequently Neither *Endamaba coli* or *Endolimax nana* ever invade the tissues of the intestine, and both are harmless parasites of man which is also true of *Iodamœba butschlii* and *Dient amaba fragilis* so that it follows that it is absolutely essential to differentiate these species from the pathogenic *Endamœba histolytica* in the diagnosis of amebiasis, which means infections with the pathogenic ameba only In this contribution an extended description of these various species would be out of place but the following brief discussion of the morphology and differential diagno- sis of these species will assist in orienting the reader in the subject and will present the most essential points in the differential diagnosis of *Endamaba histolytica*

As an ameba consists of a single cell composed of cytoplasm divided into an ectoplasm and an endoplasm and containing a nucleus or nuclei as well as ingested material of different kinds it is evident that the differentiation of genera and species must depend upon differences in the morphology and life cycle of these organisms It is obvious that in dealing with protozoa having so simple a structure generic and specific differences must be based upon very minute differences in structure and it is a fact that both generic and specific differences are based in many of these organisms upon differences in the structure of the nucleus alone

It has already been stated that the most common species of ameba living in the intestine of man are *Endamaba coli* *Endolimax nana* and *Endamœba histolytica* and it follows that in routine diagnostic work these are the species that it is especially important to differentiate *Endamœba histolytica* can be differentiated from *Endamaba coli* and *Endolimax nana* in both the trophozoite and cystic stage of development and the use of unstained preparations and iodine preparations of feces containing them can be relied upon in the differential diagnosis of these species

In the vegetative or trophozoite stage of development the morphology of the three species mentioned is distinctive but only in freshly passed stools so that it is most important that the differential diagnosis be based upon the morphology of the parasites as observed in such material

Size of the organisms is of some value in differentiation *Endamœba histolytica* in the trophozoite stage of development averages between 20 and 35 microns in diameter in dysenteric stools but is smaller in carriers *Endamœba coli* averages between 20 and 30 microns in diameter It is thus evident that size is of little importance in the differentiation of *Endamaba histolytica* and *Endamaba coli* but of much importance in differentiating these organisms from *Endolimax nana* which is a very small ameba

Motility is of much importance in differentiating the three species mentioned All move through the agency of pseudopodia formed of the ectoplasm or outer portion of the cytoplasm which are projected from the periphery of the organism and into which flows the endoplasm thus giving rise to that form of motility known as ameboid motility *Endamœba histolytica* is very actively motile in freshly passed stools the pseudopodia being projected quickly from the periphery of the body the endoplasm flowing into them so rapidly that often the distinction between it and the ectoplasm is lost the entire organism slug like in shape flowing across the field of the microscope In such rapidly moving organisms there is generally a definite polarity which may be maintained for some distance the progressing end being rounded while the opposite end is attenuated and frequently has much granular debris adherent to it The motility is progressive in character the organism moving in a definite direction for a considerable time and forcing its way through any material with which it comes into contact *Endamœba coli* is

sluggishly motile and while the motility may be progressive in character, a definite direction is not maintained for any length of time, and the slug like shape and rapidly advancing motility so characteristic of *Endamœba histolytica* is not observed *Endolimax nana* seldom presents any definite progressive motility even though observed in freshly passed stools and the pseudopodia are extruded slowly and often withdrawn without any motility resulting or there is a very slight change in the position of the ameba It is probable that any ameba observed in the stools of man that presents a rapid progressive motility in a definite direction is *Endamœba histolytica* but motility alone is not sufficient to differentiate the species

The character of the pseudopodia is of some importance in the differentiation of these species In all three the pseudopodia are formed by extrusion of the ectoplasm the pseudopodia of *Endamœba histolytica* being long and finger like in shape rapidly extruded from the periphery of the ameba and clearly differentiated from the endoplasm, if the ameba is not moving too actively, being clear and glass like in appearance If motility is rapid, the pseudopodia are no sooner extruded than the endoplasm flows into them, and the distinction is lost In *Endamœba coli* the pseudopodia are not extruded as rapidly, the distinction between the ectoplasm and the endoplasm is not as well marked and the pseudopodia are shorter more rounded in shape and never long and finger like as in *Endamœba histolytica* In *Endolimax nana* the pseudopodia usually are short and rounded although if the organism is moving with considerable rapidity they may be slender and finger like in shape but they are always much smaller than the pseudopodia of either *Endamœba histolytica* or *Endamœba coli*

Ingested material is present in all three species and its character is of diagnostic importance *Endamœba histolytica* does not ingest bacteria unless degeneration is occurring but vacuoles and bacteria may be present in ameba that have been passed for some time and are beginning to degenerate *Endamœba coli* and *Endolimax nana* both ingest bacteria and their cytoplasm generally contains numerous vacuoles even when the organisms are examined in freshly passed stools These organisms also ingest starch granules and crystalloid and granular material which may be present in the feces but this is not true of *Endamœba histolytica* Tissue cells leucocytes and red blood corpuscles may be ingested by *Endamœba histolytica* and the *ingestion of red blood corpuscles is absolutely diagnostic* of the trophozoites of this species for in many thousands of examinations the writer has never observed these cells within any other species of ameba The presence in the feces of a motile ameba containing red blood corpuscles is sufficient evidence upon which to base a diagnosis of *Endamœba histolytica* and as such organisms are always present in stools containing blood if the case is one of amebic dysentery the diagnosis is easily established If some time has elapsed between the time of

the passage of the stool and the examination *Endamœba histolytica* may appear to have ingested bacteria but in this instance the bacteria have invaded the ameba owing to degenerative changes which have occurred in its cytoplasm

A nucleus is not visible in unstained specimens of *Endamœba histolytica* in freshly passed specimens but one may become visible as degeneration occurs In *Endamœba coli* the nucleus usually is visible but usually one is not observed in freshly voided specimens of *Endolimax nana*

The diagnosis of *Endamœba histolytica* in the trophozoite stage of development is justified if an ameba is observed in the feces which is actively and progressively motile the pseudopodia being finger or bluntly blade like in appearance while the endoplasm contains red blood corpuscles It is also justified in the opinion of the writer if an ameba is present showing active, progressive motility in a definite direction and having finger like pseudopodia the cytoplasm being free from bacteria

In preparations stained with hematoxylin or other staining solutions after wet fixation the differential diagnosis of *Endamaba histolytica* rests upon the structure of the nucleus In all of the species of ameba living in the intestine of man the nucleus in stained preparations consists of a nuclear membrane which stains with more or less intensity in different species a deeply stained karyosome within the nucleus a network of delicate thread like material between the karyosome and the nuclear membrane and more or less chromatic material situated upon the internal surface of the nuclear membrane and scattered throughout the nucleus It is upon the size arrangement situation and structure of these various components of the nucleus that generic and specific differences are based and it is upon these that one must base the differentiation of *Endamœba histolytica* in stained preparations The differential features of importance in the diagnosis of the trophozoites of *Endamœba histolytica Endamœba coli* and *Endolimax nana* are given in Table IV to which the reader is referred A consideration of the differences in the structure of these species as noted in the table should enable one to make a differential diagnosis but it is well to remember that any ameba showing red blood corpuscles within its endoplasm may be diagnosed unhesitantly as *Endamœba histolytica* in stained as well as in fresh preparations

In unstained preparations one should never undertake to differentiate *Endamœba histolytica* and *Endamœba coli* in the pre cystic stage of development as both species round up become motionless and resemble one another so closely that a differential diagnosis is most difficult or impossible In properly stained preparations a differential diagnosis may be made upon differences in the structure of the nucleus

In the cystic stage of development a differential diagnosis of the three common species of ameba is possible in both unstained and stained preparations but in

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	Endamaba histolytica	*Endamaba coli*	*Endolimax nana*
	Vegetative or Trophozoite Stage Stained		
Nuclear membrane	Delicate inner surface has single layer of minute chromatin	Thicker inner surface lined with coarser chromatin dots	Intermediate in thickness chromatin rarely seen on inner surface
Karyosome	Very small Usually in center of nucleus	Twice as large situated eccentrically	Large and may be divided into one large and one small mass, situated at one side or in center of nucleus
Intranuclear chromatin	No chromatin between karyosome and membrane	Chromatin grains between karyosome and nuclear membrane	No chromatin between karyosome and membrane
Inclusions	Red blood corpuscles no bacteria in fresh specimens	No red blood corpuscles many bacteria and other material	No red blood corpuscles many bacteria
	Cystic Stage of Development Iodine Stain		
Size	6 to 20 microns average 7 to 15 microns	10 to 20 microns average 12 to 18 microns	*5 to 10 microns*
Shape	Generally spherical may be oval and rarely irregular	Spherical rarely oval or irregular	Spherical oval or ellipsoidal
Nucleus	One to four minute karyosome in center	One to eight eccentric karyosome	*One to four* large karyosome central or to one side
	Hematoxylin Stained Cysts		
Size	As in iodine stained specimens	As in iodine-stained specimens	As in iodine stained specimens
Nuclear structure	Delicate membrane minute *central* karyosome no chromatin between karyosome and membrane minute grains on nuclear membrane	Thicker membrane larger *eccentrically* located karyosome chromatin grains between nuclear membrane and karyosome and large granules of chromatin on nuclear membrane	Thick nuclear membrane large central or divided karyosome
Chromatoidal bodies	Bar oval or thick rod like masses present in about 50 per cent of the cysts	Filamentous or peculiar with square or pointed ends present in less than 10 per cent of cysts	Small granular or bacilliform masses not comparable with those seen in the other species
Nuclei number of	One to four	One to eight	*One to four*

routine diagnosis the iodine solution is always employed, while hematoxylin stained preparations are not necessary when the iodine solution gives satisfactory results

In the living unstained condition the cysts of *Endamœba histolytica* *Endamœba coli* and *Endolimax nana* all appear as colorless, refractile hyaline bodies, the cysts of *histolytica* and *coli* being usually spherical in shape, while those of *nana* are very frequently ovoid in shape The size of the cysts of *histolytica* and *coli* varies greatly and is of little value in differentiation, but the cysts of *nana* are almost always smaller than the smallest of the cysts of the other two species In unstained preparations the number of nuclei within the cysts can seldom be counted but in preparations stained with the iodine solution the nuclei can be easily distinguished and counted and the number present, together with the structure of the nucleus enables one to make a differential diagnosis of these species with little difficulty

The cysts of *Endamœba histolytica* contain from 1 to 4 nuclei, those of *Endamœba coli* from 1 to 8 nuclei and those of *Endolimax nana* from 1 to 4 nuclei Rarely a larger number of nuclei may be observed in the cysts of any of these species than the largest number present normally but this occurs so seldom as not to interfere in the least with differential diagnosis

In the iodine stained preparations of the cysts of *Endamœba histolytica* the nuclei present a very delicate hyaline membrane, and a minute, refractile dot, the karyosome, is observed at the center of the nucleus, *Endamœba coli* shows a thicker nuclear membrane and a larger refractile karyosome situated to one

TABLE IV

	Endamœba histolytica	*Endamœba coli*	*Endolimax nana*
	Vegetative or Trophozoite Stage Unstained		
Size	18 to 60 microns average 20 to 35 microns	15 to 20 microns average 20 to 30 microns	6 to 12 microns average 8 microns
Motility	Actively progressive and directional	Sluggish rarely progressive not directional	Sluggishly progressive
Pseudopodia	Finger shaped clear and glass like	Shorter and more blunt less glass like in appearance	Broad and blunt not glass like
Inclusions	Red blood corpuscles when feces contains blood no bacteria in fresh specimens	Numerous bacteria crystals and other materials no red blood corpuscles	Numerous bacteria no red blood corpuscles
Nucleus	Invisible	Visible	Visible

The *prognosis in carriers* with or without symptoms under modern methods of treatment is most excellent and the writer believes that prompt recognition and proper treatment of these individuals will be followed by the disappearance of the infection in practically 100 per cent of the cases Spontaneous recovery occurs not infrequently in this class of infections and it probably occurs much more frequently than believed by most authorities Without proper treatment the prognosis as to good health in carriers must be very guarded for while many individuals appear to carry this parasite indefinitely without the production of definite symptoms it is also true that definite symptoms occur in many cases and an amebic abscess of the liver may develop at any time For this reason the prognosis in untreated cases should be guarded and the infected individual should be told of the dangers that may arise and be urged to undergo proper treatment to eliminate the infection

The *prognosis of amebic diarrhea* if repeated attacks have occurred is not as good as that in carriers with no symptoms but with proper treatment most of these cases will recover Untreated these patients often develop the symptoms of amebic dysentery and the prognosis becomes still more unfavorable

The *prognosis of amebic dysentery* depends upon the character of the symptoms and the number of dysenteric attacks that the patient has had The mortality of amebic dysentery varies greatly in different localities being highest in the tropics and lowest in temperate regions under ordinary conditions but in cool climates the mortality may be considerable as shown in the Chicago epidemic in which there was a mortality of over 5 per cent a high mortality under modern methods of treatment In this instance the high mortality was caused by overwhelming doses of infective material contained in a water supply directly polluted by sewage Before modern methods of treatment the mortality of amebic dysentery varied from 20 to 40 per cent but under modern methods the mortality is certainly less than 5 per cent under ordinary conditions The prognosis is best in the initial attack of dysentery and becomes progressively more serious with each attack and while death now rarely occurs in patients properly treated it is true that the prognosis as regards the cure of the infection still is poor in individuals who have suffered from repeated relapses of dysentery due to *Endamaba histolytica* The prognosis in cases of amebic dysentery that have not been treated or have been improperly treated is poor for repeated attacks eventually so weaken the patient as to cause death from some intercurrent disease from the infection itself or from an amebic abscess of the liver The prognosis in fulminant or gangrenous cases of amebic dysentery always is very grave although recovery may occur even in these cases under proper treatment A high leucocytosis profound toxemia hemorrhages from the bowel fever and hiccough are all unfavorable symptoms and perforation frequently occurs in such cases

The *prognosis in chronic amebic dysentery* as to cure is unfavorable for the

side of the center of the nucleus, while the nuclei of *Endolimax nana* show a large karyosome situated either centrally or eccentrically. Oval or rounded hyaline appearing masses may occur within the cysts of *Endamœba histolytica*, the so called chromatoidal bodies, while in the cysts of *Endamœba coli* filamentous thread or crystal like rodlets, refractile in appearance, may occur.

In preparations wet fixed and stained with hematoxylin all of the structures visible in iodine stained preparations are very beautifully differentiated and can be still more easily recognized. Such preparations, however, are not necessary for routine differential diagnosis, as with the iodine stain the number of nuclei characteristic of each species as well as the nuclear membrane, the karyosome and the chromatoidal bodies are well demonstrated and, except in very rare instances, sufficiently so for a differential diagnosis to be made. Table IV contains all of the essential differential points between *Endamœba histolytica*, *Endamœba coli* and *Endolimax nana* which have been discussed.

Sigmoidoscope in the Diagnosis of Amebiasis

Sigmoidoscopy is of value in the diagnosis of amebiasis but is useful only in cases in which lesions are present in the rectum or sigmoid. Its routine employment to the exclusion of other methods is not recommended, and it should be used only in case stool examinations have proven negative by approved methods and after repeated examinations. It is often useless in latent or symptomless infections, for in such infections the rectum or sigmoid are seldom involved to the extent that characteristic macroscopic lesions are present in these regions. If lesions are present, their true character can be ascertained only by the demonstration of *Endamœba histolytica* in material removed from the lesions, and it has been the writer's experience that in the vast majority of cases, if lesions are present, the amebæ can be demonstrated in the feces. In rare instances a sigmoidoscopy will enable one to demonstrate the parasite when fecal examinations have failed, but the procedure certainly is not necessary in routine diagnosis unless repeated fecal examinations have proven negative in a suspected individual.

Prognosis

The prognosis in amebiasis depends upon the extent of the lesions produced by *Endamœba histolytica*, but at the present time it is excellent in the majority of infections with this parasite. Owing to insufficient or faulty data our knowledge of the morbidity and mortality of amebiasis in the United States and indeed throughout the world is limited and imperfect. It is certainly true that in temperate regions the infection is much less fatal than in the sub tropics or tropics, while the morbidity is also much higher in the latter regions.

water depends essentially upon the proper disposal of sewage In rural districts it is just as important to insist upon the installation of properly constructed and maintained privies in the prevention of amebiasis as in the prevention of hookworm infection for the indiscriminate di posal of fecal material upon the ground in the vicinity of dwellings inevitably will result in the pollution of the local well or spring and the consequent infection of those drinking the water provided a carrier of *Endamaba histolytica* be present

Water obtained from a properly constructed and operated public filtration plant is harmless as it has been repeatedly shown that sand filtration removes the cysts of *Endamaba histolytica* but such water may become a transmitting agent after leaving the plant by contamination locally through back syphonage cross-connections in plumbing or breaks in sewers and the possiblity of such contamination should be avoided by the installation of proper plumbing Faulty plumbing undoubtedly was the cause of the extensive epidemic of amebic dysentery which occurred in Chicago in the two hotels where mo t of the case orig inated, and similar conditions as regards plumbing undoubtedly exist in many of our hotels and public and private institutions in other parts of the country In the prevention of amebiasis the most stringent measures should be enforced against cross connections between water supplies which are safe for domestic use and those unfit for domestic use

Chlorination of water as usually applied in sterilizing it for intestinal bacteria is useless in the prevention of amebiasis as the cysts of *Endamaba histolytica* are not destroyed by the amount of chlorine used in sterilizing water supplies However for water sterilization in camps and in the field where the method can be applied overchlorination and dechlorinization afterwards is an efficient measure while for the sterilization of water in canteen two halazone tablets dissolved in the water in the canteen and allowed to remain in contact for 30 minutes before using the water will kill the cysts unless the water is colored or turbid when four tablets should be employed If the Lyster bag is employed in the field and calcium hypochlorite is used enough of the latter should be added to provide one part per million of residual chlorine after contact for 10 minutes An additional ampule of calcium hypochlorite should then be added and the water allowed to stand for 30 minutes before use It has been determined by the United States Army that a concentration of chlorine sufficient to give two parts per million of residual chlorine after 30 minutes contact will destroy the cysts of *Endamaeba histolytica*

Whenever it is impossible to chlorinate water in the manner recommended above it always should be boiled before use in all regions where the water is of unknown origin or subject to fecal contamination After all boiling is by far the safest method of killing the cysts of this ameba and the most simple under ordinary domestic conditions

organisms are so located in the coats of the intestine as to be inaccessible to drugs and acute attacks of dysentery continue despite the best of treatment Fortunately, chronic amebic dysentery is daily becoming less frequent owing to more prompt recognition of amebic infections and to proper treatment with specific remedies

The *prognosis of amebic abscess of the liver* always is grave, and many deaths occur despite the best methods of treatment Prior to the introduction of emetine hydrochloride in the treatment of this condition the mortality of abscess of the liver was over 70 per cent but under modern surgical treatment and the use of emetine the mortality has been reduced to below 15 per cent The prognosis varies with the number of abscesses being most unfavorable when multiple abscesses are present Thus Strong (1925) states that Sambuc found that the mortality was 23 per cent in patients having a single abscess, 45 per cent in patients having 2 abscesses 90 per cent in patients having 3 abscesses and 100 per cent in patients having more than 3 abscesses The writer has found that practically every case of multiple amebic abscess of the liver terminates fatally unless the abscesses can be drained, and it is doubtful that the mortality of amebic abscess of the liver is ever less than 20 per cent if one includes cases of multiple abscess in the statistics If a large single abscess be present which can be aspirated and drained, the prognosis usually is excellent If the presuppurative stage of liver abscess be recognized and properly treated, the prognosis is excellent as such treatment usually is followed by cure

The *prognosis of amebic abscess of the lung* should be guarded, but if promptly discovered and treated with emetine usually it is favorable The *prognosis of amebic abscess of the brain* is hopeless If properly treated *amebiasis of the appendix* and of *the skin* have a good prognosis but operations upon the appendix in the presence of acute amebic dysentery are often followed by death The proper treatment of the intestinal amebiasis with emetine will result in the disappearance of the symptoms of appendicitis if the condition is caused by *Endamœba histolytica* as well as in the cessation of the dysenteric symptoms

Prophylaxis

The prophylaxis of amebiasis consists in the protection of food and drink from contamination with the cysts of *Endamœba histolytica* Such contamination may result from sewage polluted water the handling of food or drink by food handlers who are carriers of the parasite the contamination of garden vegetables or fruits through the use of sewage for fertilization purposes and the contamination of food by the droppings of infected flies that have fed upon material containing the cysts of *Endamœba histolytica*

Water Transmission — The prevention of the transmission of amebiasis by

water depends essentially upon the proper disposal of sewage In rural districts it is just as important to insist upon the installation of properly constructed and maintained privies in the prevention of amebiasis as in the prevention of hookworm infection for the indiscriminate disposal of fecal material upon the ground in the vicinity of dwellings inevitably will result in the pollution of the local well or spring and the consequent infection of those drinking the water provided a carrier of *Endamæba histolytica* be present

Water obtained from a properly constructed and operated public filtration plant is harmless as it has been repeatedly shown that sand filtration removes the cysts of *Endamaba histolytica* but such water may become a transmitting agent after leaving the plant by contamination locally through back syphonage cross-connections in plumbing or breaks in sewers and the possibility of such contamination should be avoided by the installation of proper plumbing Faulty plumbing undoubtedly was the cause of the extensive epidemic of amebic dysentery which occurred in Chicago in the two hotels where most of the cases originated and similar conditions as regards plumbing undoubtedly exist in many of our hotels and public and private institutions in other parts of the country In the prevention of amebiasis the most stringent measures should be enforced against cross connections between water supplies which are safe for domestic use and those unfit for domestic use

Chlorination of water as usually applied in sterilizing it for intestinal bacteria is useless in the prevention of amebiasis as the cysts of *Endamaba histolytica* are not destroyed by the amount of chlorine used in sterilizing water supplies However for water sterilization in camps and in the field where the method can be applied overchlorination and dechlorinization afterwards is an efficient measure while for the sterilization of water in canteens two halazone tablets dissolved in the water in the canteen and allowed to remain in contact for 30 minutes before using the water will kill the cysts unless the water is colored or turbid when four tablets should be employed If the Lyster bag is employed in the field and calcium hypochlorite is used enough of the latter should be added to provide one part per million of residual chlorine after contact for 10 minutes An additional ampule of calcium hypochlorite should then be added and the water allowed to stand for 30 minutes before use It has been determined by the United States Army that a concentration of chlorine sufficient to give two parts per million of residual chlorine after 30 minutes contact will destroy the cysts of *Endamæba histolytica*

Whenever it is impossible to chlorinate water in the manner recommended above it always should be boiled before use in all regions where the water is of unknown origin or subject to fecal contamination After all boiling is by far the safest method of killing the cysts of this ameba and the most simple under ordinary domestic conditions

organisms are so located in the coats of the intestine as to be inaccessible to drugs and acute attacks of dysentery continue despite the best of treatment Fortunately chronic amebic dysentery is daily becoming less frequent owing to more prompt recognition of amebic infections and to proper treatment with specific remedies

The *prognosis of amebic abscess of the liver* always is grave, and many deaths occur despite the best methods of treatment Prior to the introduction of emetine hydrochloride in the treatment of this condition the mortality of abscess of the liver was over 70 per cent but under modern surgical treatment and the use of emetine the mortality has been reduced to below 15 per cent The prognosis varies with the number of abscesses, being most unfavorable when multiple abscesses are present Thus Strong (1925) states that Sambuc found that the mortality was 23 per cent in patients having a single abscess, 45 per cent in patients having 2 abscesses 90 per cent in patients having 3 abscesses and 100 per cent in patients having more than 3 abscesses The writer has found that practically every case of multiple amebic abscess of the liver terminates fatally unless the abscesses can be drained, and it is doubtful that the mortality of amebic abscess of the liver is ever less than 20 per cent, if one includes cases of multiple abscess in the statistics If a large single abscess be present which can be aspirated and drained the prognosis usually is excellent If the presuppurative stage of liver abscess be recognized and properly treated, the prognosis is excellent as such treatment usually is followed by cure

The *prognosis of amebic abscess of the lung* should be guarded, but if promptly discovered and treated with emetine usually it is favorable The *prognosis of amebic abscess of the brain* is hopeless If properly treated *amebiasis of the appendix* and of *the skin* have a good prognosis but operations upon the appendix in the presence of acute amebic dysentery are often followed by death The proper treatment of the intestinal amebiasis with emetine will result in the disappearance of the symptoms of appendicitis if the condition is caused by *Endamœba histolytica* as well as in the cessation of the dysenteric symptoms

PROPHYLAXIS

The prophylaxis of amebiasis consists in the protection of food and drink from contamination with the cysts of *Endamœba histolytica* Such contamination may result from sewage polluted water the handling of food or drink by food handlers who are carriers of the parasite the contamination of garden vegetables or fruits through the use of sewage for fertilization purposes and the contamination of food by the droppings of infected flies that have fed upon material containing the cysts of *Endamœba histolytica*

Water Transmission —The prevention of the transmission of amebiasis by

The occurrence of cases of amebic dysentery in individuals who have eaten at any public eating place should be a signal for the survey of all the food handlers of such eating place for infections with *Endamœba histolytica* and also for a survey of the plumbing for the possible occurrence of cross connections between potable and polluted water supplies While the writer does not believe that it is feasible to examine all food handlers employed in all public eating places he does believe that this measure should be enforced wherever there is a suspicion that any out break of amebic dysentery has been caused by food handlers in a specific eating place and that such surveys are practicable and fall within the duties of Health Departments

The detection of infected food handlers depends upon the demonstration of *Endamœba histolytica* in the stools and this requires the services of a trained laboratory technician Unfortunately the number of technicians who are qualified in this respect is comparatively small at present so that the training of laboratory personnel in the differentiation of this ameba from the other species occurring in the intestine of man is most essential if reliable results are to be obtained in any survey of food handlers

Sewage in Fertilization —The prevention of the contamination of garden truck through the use of sewage in fertilization depends upon the enforcement of laws forbidding this practice and the avoidance of uncooked fruit and vege tables in regions where this practice is not forbidden by law It is possible to render fruits and vegetables safe that have been thus fertilized by immersing them in boiling water for 30 seconds the temperature being kept at the boiling point during this time In thus treating leafy vegetables as lettuce cabbage spinach kale etc it is necessary to separate the leaves washing each in running water and then immersing for the time stated in boiling water After this treat ment the fruits or vegetables may be freshened by immersing them in ice cold water or placing them in the ice box *The safest plan is to avoid the ingestion of all uncooked garden truck or fruits in any region where human excrement is used in fertili ation*

Flies in Transmission —The prevention of the transmission of amebiasis by flies depends upon the protection of food and drink from these insects The screening of dining rooms and mess halls from flies and the screening of all food supplies exposed outside screened rooms should be rigidly enforced and proper measures should be taken to prevent the breeding of these insects so as to decrease the number of flies

The discovery of the lethal effect of dichloro-diphenyl trichlorethane or DDT as it is known in the trade upon flies has added a potent weapon for use in the prevention of amebiasis There is no question that flies do act as transmitters of amebiasis and the proper screening of dining rooms mess halls kitchens and the proper disposal of garbage in the past has caused the disappearance of amebiasis

In regions, where amebiasis is known to be prevalent and water may be contaminated, it should be treated chemically or boiled, and one should avoid eating raw fruits or vegetables that may have come in contact with contaminated water Salad vegetables and fruits are most important in the transmission of amebiasis if they have been washed in contaminated water, and salads containing them should never be eaten in regions where amebiasis is prevalent

Food Handlers — The prevention of infection with *Endamœba histolytica* by food handlers consists in the detection and proper treatment of carriers of this parasite who are thus employed Ideally no one who is a carrier of this ameba should be allowed to handle food, but owing to the very large number of such carriers it is quite evident that their examination and removal from employment while under treatment usually is impossible

The economic questions involved in carrier surveys and the treatment of those found infected force the conclusion that only in certain localities and under certain conditions is a general survey of food handlers possible and that one must be content with only a partial realization of the ideal in most places How much may be accomplished with the means available will always remain a local question but the writer believes that it is perfectly feasible to examine food handlers employed in hotels restaurants and other public eating places in certain localities and to treat properly those that are found infected with *Endamœba histolytica* Removal from their occupation is not necessary, if they are instructed as to the means of preventing the contamination of the food which they handle for treatment may be administered without interfering with their duties Treatment should be administered as soon as the infection is discovered, and the writer believes that, under proper supervision, an infected food handler may continue his occupation without being a danger to others, provided he is instructed in the simple measures of personal hygiene which will prevent the transmission of the infection to others

If infected food handlers are discovered it is preferable that they be removed from their occupation if possible and properly treated the treatment being controlled by repeated microscopic examination of the stools and the food handler not being allowed to resume his occupation until at least three examinations made at daily intervals and commencing a week after cessation of treatment, are reported as negative Such food handlers should be instructed to wash their hands thoroughly after using the toilet and to avoid depositing their feces where flies might gain access to them or where there is any chance of their contaminating food or water If it is not possible to remove the infected food handler from his occupation instruction should be given him as to the means of preventing infection of others through food or drink, and proper treatment should be instituted at once

to believe that sanitary conditions are poor and the chances of becoming infected with *Endamaeba histolytica* are great as in the case of tourists in Mexico where amebiasis is very prevalent many persons become infected each year through the ingestion of contaminated material while traveling in that country

In conclusion the writer would call attention to the fact that personal hygiene is an important factor in the prevention of amebiasis and the simple habit of thoroughly washing the hands before handling food and after the use of the toilet undoubtedly would greatly reduce the prevalence of this important infection

TREATMENT

The treatment of amebiasis includes the treatment of carriers of *Endamœba histolytica* with or without symptoms those suffering from amebic diarrhea or enteritis those presenting the symptoms of acute or chronic amebic dysentery and the treatment of amebic hepatitis or amebic abscess of the liver and other organs It is now recognized that the treatment of the symptom-complex of amebiasis known as amebic dysentery comprises but a very small part of the treatment of amebiasis and that the proper treatment of carriers and of those having slight symptoms of the infection is vastly more important than the treatment of dysentery for the proper treatment of such infections will prevent the development of dysentery symptoms

While modern research in the therapeutics of amebiasis has led to the discovery of several drugs that may be considered as almost specific it should be understood that at present we possess no single drug or any single method of treatment which will eliminate infections with *Endamœba histolytica* in every case and in the following discussion of the treatment of this condition the writer will describe the methods that he has found most successful and will mention but briefly other methods that have proven of value in the hands of other observers

Treatment of Carriers of Endamœba histolytica — The evidence that is available proving that in carriers of *Endamœba histolytica* both microscopic and macroscopic lesions are present in the intestine even though there may be no symptoms of the infection demonstrates that every individual harboring this parasite should be treated and rid of the infection The treatment of carriers with or without symptoms is most important from both a prophylactic and remedial standpoint and it is obvious that any treatment which demands rest in bed is not suitable in such cases owing to the mildness of the symptoms which may be present or to their entire absence Thus the ideal drug for the treatment of such individuals would be one which could be administered with success without interrupting the occupation of the individual taking it and fortunately we possess several such drugs that are most efficient in the treatment of amebiasis in this

as a public health danger but now that DDT is available we have an added method of prevention that is most efficient

In the prevention of amebiasis DDT should be used as a residual spray in a 5 per cent solution in kerosene and all surfaces upon which flies usually rest should be sprayed with this solution The spray should be applied at the rate of 200 mgm per square foot (1 quart per 250 square feet) to walls, ceilings, screens, light fixtures garbage racks and any surface upon which flies might alight One spraying a month is sufficient as the lethal effect upon flies will continue for even longer than one month as shown by conclusive experiments If pit latrines are in use, they should be sprayed upon the walls the inside and outside of the latrine box and the walls and screens of the building containing the latrines In order to prevent the breeding of flies in such latrines the contents should be sprayed with the DDT residual spray at the rate of 2 ounces per latrine box hole, care being taken that it is applied evenly This treatment should be repeated twice a week if necessary

Education — The education of the public as to the methods of transmission of amebiasis and the simple rules of personal hygiene that will prevent such transmission is a prophylactic measure of considerable value The public should be informed that amebiasis and amebic dysentery are not tropical conditions, the methods of transmission and the part played by carriers in the transmission of this infection should be stressed the importance of personal hygiene and the proper disposal of feces in the prevention of the infection should be emphasized while the medical profession may assist greatly in prophylaxis by the proper treatment of those infected thus preventing the dissemination of the infection by carriers and the development of serious lesions and symptoms in the infected individual

Drug Prophylaxis — In 1940 the writer suggested that the iodine compound known as diodoquin which contains 63 9 per cent of iodine, is slowly absorbed from the intestine and produces no toxic symptoms when administered in thera peutic dosage might be found to be useful in the prevention of amebiasis under certain conditions as in traveling in regions where this infection is known to be very prevalent The drug is furnished in tablets each containing 0 21 gm (gr 3 2) and it was recommended that 7 of these tablets be taken daily, 2 after breakfast and lunch and 3 after dinner The drug is tasteless, non toxic and has been found by numerous investigators to be very efficient in the treatment of amebiasis At the present time the writer believes that smaller doses may be efficient in prophylaxis and that 2 tablets taken after breakfast and after dinner would be sufficient to destroy any amebae which might have been ingested during the day and that this treatment could be continued for 1 month or more In the opinion of the writer diodoquin should prove to be of great value in the preven tion of amebiasis in the case of travelers in endemic regions, where there is reason

and D'Antoni recommend 3 tablets 3 times a day for 20 days if symptoms of diarrhea or dysentery be present but in the case of symptomless carriers this larger dosage is not essential

In some carriers who have proven resistant to chiniofon the administration of vioform is followed by the disappearance of the infection Vioform which has been on the market for some years as a surgical antiseptic, was first recommended in the treatment of amebia is by David Johnstone Reed and Leake (1933) Chemically vioform is iodochlorhydroxyquinoline and contains not less than 37 5 and *not more than* 41 5 per cent of iodine and not less than 11 5 and not more than 12 2 per cent of chlorine thus containing about twice as much iodine as chiniofon It is very slightly toxic in therapeutic doses producing palpitation dyspnea headache diarrhea with mucus and blood in the stools in three cases that have been reported but it is considered a safe drug to use in all except weakened individuals The writer has observed its use in many carriers without the appearance of any toxic symptoms

Vioform is administered by the mouth in gelatin capsules each containing 0 25 gm (4 grains) and one capsule is given three times a day for 10 days and the same doses repeated for 10 days after an interval of one week without treatment Those who have used this drug extensively state that it is a most efficient amebacide and eliminates infection with *Endamœba histolytica* in a very large percentage of the individuals to whom it has been administered

In carriers who have not responded to treatment with either chiniofon diodoquin or vioform a course of treatment with carbarsone may prove successful. This is an arsenical compound and was introduced by Anderson and Reed (1931) as a specific in the treatment of amebiasis Chemically it is 4-carbaminophenyl arsonic acid and is probably the least toxic of any of the arsenicals which have been recommended in the treatment of amebiasis Toxic symptoms may occur and are tho e usually observed in poisoning by arsenic but reports are few in which any serious toxic symptoms have been observed and the writer has not observed such symptoms using the drug in the dosage recommended by Anderson and Reed Carbarsone is administered in gelatin capsules each capsule containing 0 25 gm (4 grains) A capsule is given twice a day for 10 days and if the cysts of *Endamœba histolytica* have not disappeared from the stools after a single course of treatment it may be repeated after an interval of 10 days This drug must be administered under the close supervision of a physician and is not as well suited for administration to large numbers of people as chiniofon which may be safely used without the necessity of consulting the physician during the course of treatment

In treating carriers without symptoms and mild infections the writer recommends a course of treatment with either chiniofon or diodoquin and if this is unsuccessful a course of treatment with carbarsone should be given The results

class of cases The drugs which are available for this purpose are chiniofon, diodoquin carbarsone, vioform and treparsol

In the writer s experience chiniofon has proven to be the most efficient and safest drug for the treatment of carriers with or without symptoms Chiniofon (yatren or anayodin) which chemically is sodium iodoxyquinolinsulfonate, depends for its amebacidal properties upon the iodine which it contains which varies from 26 to 28 per cent It is practically non toxic in therapeutic doses, and the writer has never observed any serious symptoms of toxicity in his experience covering several years use of the drug In many individuals the full therapeutic dose gives rise to a rather severe diarrhea for the first three or four days of administration which sometimes necessitates a reduction in the dose, but the fact that scores of thousands of patients have been treated with this drug since its introduction in 1921 as an amebacide without any serious toxic symptoms being reported and not a single death, when properly administered, demonstrates its harmlessness It has been shown by several investigators that this drug acts directly upon the trophozoites of *Endamaba histolytica* in comparatively low dilutions killing them in vitro and the results obtained clinically demonstrate that in the body the drug is a very efficient amebacide and if properly administered is curative in a large percentage of amebic infections

Chiniofon is furnished in tablets or pills each containing 0 25 gm (4 grains), and the dose for an adult varies from 3 to 4 pills three times a day for a period of from 8 to 10 days usually for 8 days As the full dose of 4 pills three times a day often causes a severe diarrhea it is best to start with 3 pills three times a day and increase to the full dose if the drug is well borne During administration the patient should avoid eating rich or too sweet food or those foods which are known to disagree with the individual The dose of chiniofon in children should be governed according to the age of the child This drug may be administered without interfering with the patient s occupation, and a single course of 8 to 10 days treatment will eliminate the infection in the vast majority of carriers while a second course of treatment with the drug repeated after an interval of 10 days usually eliminates the infection in the remainder

A compound which recently has been found to be practically specific in the treatment of carriers of *Endamæba histolytica* is diodoquin This is a tasteless powder chemically 5 7-diodo-8-hydroxy quinoline containing 63 9 per cent of iodine The reports of Tenney (1936) Silverman (1937), Hummel (1937-1940), D'Antoni (1942-1943) and others have demonstrated that this compound is very efficient as an amebacide and some of these authorities prefer it to chiniofon, as it does not produce any unpleasant symptoms It is furnished in tablet form, each tablet containing 0 21 gm (gr 3 2) and the dose in the case of carriers or individuals having mild symptoms of the infection is 6 or 7 tablets daily, administered in divided doses after meals and continued for 20 days Both Hummel

wrist, ankle, or toe-drop arrhythmias nausea vomiting and prostration if given in large doses or over a long period of time The writer has observed scores of individuals suffering from emetine poisoning and several deaths from cardiac failure following prolonged administration of this drug The old idea that emetine is the best of all specifics in the treatment of amebic infections is still strong in the minds of large numbers of practitioners and this has led to great abuse of a drug that is most valuable in treatment of the symptoms of amebiasis but of comparatively little value in eliminating amebic infection

Emetine acts directly upon the trophozoites of *Endamœba histolytica* killing them in cultures in dilutions of 1–25 000 but in the experience of the writer and others *it is far inferior to other amebacides like chiniofon vioform or carbarsone* in actually curing amebic infections In 130 cases of amebic dysentery observed by the writer and treated with emetine hydrochloride alone in many cases two complete courses of the drug being administered no less than 60 per cent still showed cysts of *Endamœba histolytica* at the time of completion of a single course of injections and no less than 81 per cent became carriers of the infection It is believed that this drug if administered in safe dosage does not cure amebiasis in more than 10 to 15 per cent of the individuals to whom it is administered for this purpose

However feeble as is the curative action of emetine it does have a most striking influence in modifying and causing the disappearance of the symptoms of diarrhea or dysentery produced by the parasite For this reason emetine should be used in the treatment of acute amebic dysentery until the acute symptoms subside but the dosage should never exceed 0 065 gm (1 grain) per day administered subcutaneously, and this dose should not be continued for longer than 12 days

The writer s treatment of acute amebic dysentery is as follows

The patient should be given 0 065 gm (1 grain) of emetine hydrochloride injected subcutaneously until the dysenteric symptoms subside and the stools become *mushy or semi formed but this dose should not be exceeded or admin* istered for more than 12 days After the subsidence of the dysenteric symptoms chiniofon is administered as recommended in the case of carriers or those suffering from enteritis In the majority of cases in from 4 to 8 days after the beginning of the administration of emetine the dysenteric symptoms will have disappeared and the course of treatment with chiniofon may be begun During treatment with emetine the patient should be watched for any toxic symptoms characteristic of this drug and if any appear it should be stopped and chiniofon carbarsone or vioform substituted Emetine should never be administered intravenously nor is it necessary in the writer s experience to combine oral administration of emetine with the hypodermic injections

If the dysenteric symptoms are not severe it is not necessary to employ

of treatment should be checked by stool examinations for the trophozoites or cysts of *Endamœba histolytica* and after the completion of the treatment and the apparent elimination of the infection a follow up stool examination should be made at weekly intervals for at least 1 month and thereafter at the end of 3 months If at any time the parasite is found to be present in the stools, another course of treatment with one of these compounds should be administered and the stools again checked as directed above During any of these treatments the patient need not interrupt his usual routine, and rest in bed is unnecessary

Treatment of Amebic Diarrhea — In the treatment of those infections with *Endamœba histolytica* characterized by repeated attacks of diarrhea lasting for several days rest in bed should be insisted upon during the period of diarrhea, and diodoquin should be administered 3 tablets 3 times a day and continued for 20 days even though the diarrhea ceases This compound is to be preferred to chiniofon as the latter may increase the diarrhea, although it usually eliminates the infection If the diarrhea is persistent or very severe, emetine hydrochloride may be administered subcutaneously in doses not to exceed 0 065 gm (gr 1) a day for not more than 5 or 6 days If the patient is seen between attacks of diarrhea, the treatment should be the same as that recommended for carriers of *Endamœba histolytica* Repeated courses with diodoquin or the employment of vioform or carbarsone may be necessary in resistant infections During the continuance of diarrheal symptoms the diet should be like that recommended below in cases of acute amebic dysentery and during convalescence it should be limited to easily digested foods and overeating and the use of alcoholics should be avoided

Treatment of Acute Amebic Dysentery — The most useful drugs in the treatment of acute amebic dysentery have been found by the writer to be emetine hydrochloride and chiniofon

Emetine was first suggested in the treatment of amebiasis by Vedder (1912) and was first employed in the treatment of acute amebic dysentery by Rogers (1912) It is one of the alkaloids of ipecacuanha, a well known amebacide and was for many years considered a specific in the treatment of amebiasis It is now known that emetine alone cures but a small percentage of amebic infections, but it is most efficient in relieving the acute symptoms in dysentery caused by *Endamœba histolytica* It should not be depended upon alone in the treatment of amebiasis but should be employed only for the alleviation of acute dysenteric symptoms and should never be employed in the treatment of carriers or cases of amebiasis in which severe diarrhea or dysentery does not occur

Emetine is a toxic drug and should be employed with caution It is cumulative in its action and has a very powerful influence upon the cardiac muscle producing severe myocarditis if used in too large doses or over too long a period of time In addition, it may cause severe diarrhea, great muscular weakness,

has been a marked loss of mucous membrane through ulceration large areas being replaced by fibrous scar tissue which prevents the absorption of fluids attacks of diarrhea may continue even though the amebic infection may have been eliminated

The results of treatment of amebic diarrhea and dysentery should be checked by stool examinations in the same manner as the treatment of carriers and if either trophozoites or cysts of *Endamœba histolytica* reappear in the stools the treatment should be repeated At least three negative examinations should be secured a week apart before the patient is considered as cured and thereafter the feces should be examined once a month for three months in order to detect a relapse if it should occur

The methods of treatment of the various phases of amebiasis which have been detailed are those which the writer has found most efficient in curing the infection but there are several other drugs that have been used in the treatment of this condition that have been proven efficient in the hands of other observers and these will now be briefly discussed

Emetine Bismuth Iodide —This combination consists of emetine 25 per cent bismuth 12 per cent and iodine 58 per cent It has been used very extensively in the treatment of amebiasis by English authorities with excellent results but it cannot be used in the treatment of carriers as the patient must be at rest in bed while undergoing treatment The toxicity of this combination is due to the emetine present and sometimes the administration has to be stopped owing to the development of extreme nausea and vomiting or cardiac weakness The dose is 0 2 gm (3 grains) administered in gelatin capsules once a day for 12 days It is best given at night with hot tea or broth the patient laying flat in bed with the head level with the body

During the first night or two nausea is almost invariably present and salivation and vomiting may occur throughout the course of the treatment The treatment should be persisted in until the 12 daily doses have been administered unless toxic symptoms develop After completion of the treatment the patient is kept in bed for at least three days and should be warned against overexertion for several weeks after resuming his usual occupation A second course of treatment may be given after an interval of a week if the stools are found to be positive for *Endamœba histolytica* Owing to the necessity of confinement to bed during administration and the occurrence of the disagreeable symptoms which always accompanies its administration the writer believes that emetine bismuth iodide has practically no place in the modern therapy of amebiasis

Acetarsone (*Stovarsol*) —This drug has been largely used in the treatment of amebiasis but has been practically replaced by carbarsone which is less toxic Chemically acetarsone is acetylaminohydroxyphenylarsonic acid and contains from 27 1 to 27 4 per cent of arsenic It can be used in the treatment of carriers

emetine in the treatment of amebic dysentery, as chiniofon alone is often successful in the treatment of such mild attacks It should be administered in 0 5 gm (7 5 grains) doses three times a day for 8 to 10 days, as the full dose recommended for carriers or mild diarrheal cases is often poorly borne owing to the increase in the dysenteric symptoms which may be caused by the larger doses If the use of emetine is contraindicated in severe amebic dysentery, and chiniofon is used alone the best results are obtained by the administration of the drug by mouth as recommended above and the injection rectally of 200 c c of a 2 per cent warm water solution of chiniofon which should be retained for as long as possible, the chiniofon enema being given once a day The combined treatment by mouth and with chiniofon enemas should be continued for from 8 to 10 days, the patient being kept in bed during this period

If the methods of treatment described are unsuccessful in eliminating the infection in acute amebic dysentery other methods should be employed, and the drugs that have been found to be most useful are diodoquin, vioform and carbarsone administered as already described in the treatment of carriers of *Endamœba histolytica* The writer believes that failure to respond to an iodine compound as chiniofon indicates that an arsenical compound should be used, and of the arsenicals carbarsone undoubtedly is the best If it is employed and the patient does not show improvement it can be given as a retention enema consisting of 200 c c of a 2 per cent solution of sodium bicarbonate containing 1 per cent of carbarsone Such an enema should be administered daily for at least 5 days and should be retained as long as possible This form of treatment is not curative and should be followed by the oral administration of the drug as usual Anderson and Reed state that the dysenteric symptoms rapidly disappear after treatment with carbarsone by rectum as a retention enema Diodoquin has been found to be efficient also in the treatment of acute amebic dysentery after a preliminary treatment with emetine in the more severe cases, while in mild cases of dysentery diodoquin alone is excellent administered in a dosage of 3 tablets 3 times a day for a period of 20 days

Treatment of Chronic Amebic Dysentery — The treatment of the chronic form of amebic dysentery, if the patient is seen during an acute exacerbation of dysentery should be that recommended for acute amebic dysentery while if the patient is seen between the dysenteric attacks, he should be given a course, or courses, of chiniofon as recommended in the treatment of carriers of *Endamœba histolytica* As already stated the results of treatment in patients, who have had many relapses of acute dysentery very frequently are unsatisfactory with any method of treatment so that generally it is necessary to repeat courses of treatment with any of the drugs that may be used in order to control the symptoms at least but one should not be disappointed if it be found impossible to cure the infection in these cases It should also be remembered that, if there

in very large doses emetine periodide auremetine, chaparro amargosa, di hydranol, the arsphenamines various salts of mercury silver and quinine, rivanol amibiarsone and gavano Almost every month some new synthetic preparation is introduced for the treatment of this infection and it is probable that eventually we will have much more specific preparations than we possess at the present for the treatment of amebiasis but the writer believes that chiniofon vioform and carbarsone are much more efficient than any of the other remedies mentioned and one may safely rely upon them in the treatment of this condition

General Treatment —As already stated in the treatment of carriers with or without symptoms confinement to bed is not necessary during treatment but if severe diarrhea or dysentery be present the patient should be confined to bed In carriers a special diet is not necessary during treatment but during acute diarrheal or dysentery symptoms it is best to withhold all food except egg albumin or broths for a period of two or three days when if the dysenteric symptoms have improved pure milk malted milk and junket may be added to the diet After the stools are reduced in frequency and become less fluid in consistence, eggs soft puddings milk toast and a semi fluid diet should be given and a full diet very gradually resumed after the stools have become normal in appearance Foods that are known to irritate the intestine should be avoided as well as those containing much roughage and the use of alcoholics should be absolutely prohibited

The administration of tonics during convalescence is useful and iron should be administered, preferably in the form of Blaud s pills or ferric ammonium citrate A change of climate if the patient lives in the tropics is a very important remedial measure and in individuals who are living in the tropics a change to temperate regions often is almost as valuable in eliminating amebic infection as medical treatment owing to the increase in natural resistance that follows such a change in climate

Treatment of Amebic Hepatitis and Amebic Abscess of the Liver —The proper treatment of the presuppurative stage of amebic abscess of the liver and amebic hepatitis is most important as the early recognition and treatment of these conditions will prevent the development of liver abscess The occurrence of a leucocytosis fever and discomfort or pain over the hepatic region in patients suffering from intestinal amebiasis is almost diagnostic of amebic hepatitis and beginning abscess formation and if these symptoms should develop the patient should be given a subcutaneous injection of 0 065 gm (1 grain) of emetine hydrochloride once a day for not to exceed 12 days If the symptoms are caused by invasion of the liver by *Endamœba histolytica* such treatment should be followed by the disappearance of the fever within about a week after beginning treatment and there should be a marked drop in the leucocytosis or a return to a normal count

as confinement to bed is not necessary during its administration, but its toxicity is considerable colic diarrhea, puffiness of the face and eyelids, fever and erythematous skin eruptions being sometimes observed during its administration. The drug is furnished in tablet form, and the dose is one tablet or 0 25 gm (4 grains) by mouth, three times a day for seven days, cessation of treatment for one week and then one tablet three times a day for one more week The writer used this drug extensively in the treatment of amebiasis prior to the introduction of chiniofon carbarsone and vioform and found that the dose recommended above can be cut in half with practically as good results in treatment and with the elimination of toxic symptoms which not infrequently follow the full dose If this drug be used one half tablet should be given as indicated above instead of one tablet The efficiency of acetarsone in the treatment of amebiasis equals that of carbarsone which is also an arsenical, but the latter drug is less toxic and should be preferred in treatment

Treparsol — This drug which was highly recommended by Brown (1928) in the treatment of amebiasis is an arsenical preparation, chemically a formylated acid derived from meta amino para oxyphenyl arsenic acid, and is furnished in tablets each containing 0 25 gm (4 grains) The dose is 0 25 gm (4 grains) three times a day with meals for 4 days cessation of the treatment for 10 days and finally 0 25 gm three times a day for 4 days Brown states that the tablets should be chewed with food in order to secure greater dispersion of the arsenic. The toxicity of this drug is said to be low and its efficiency in the treatment of amebiasis superior to that of acetarsone, which is more toxic than treparsol

Kurchi Bark — In India the bark of a small deciduous tree (*Holarrhena antidysenterica*) has long been known to be efficient in the treatment of dysentery This bark known as Kurchi Conessi or Tellicherry bark, contains four alkaloids, conessine holarrhenine kurchicine and kurchine At the present time tablets containing kurchi bark are available the dose being 0 65 gm (10 grains) three times a day while a combination of the total alkaloids with bismuth and iodine, known as kurchi bismuthous iodide has been highly recommended by Acton and Chopra (1929) in doses varying from 0 25 gm (4 grains) by mouth twice a day for 10 days in chronic amebic infections to 0 65 gm (10 grains) twice a day for 10 days in severe acute infections In these doses they state that no toxic symptoms have been noted and the results of treatment have been excellent The bark may also be administered by mouth in the form of the fluid extract the dose being 8 c c (2 drachmes) three times a day and continued for from 4 to 6 weeks in chronic infections The administration of kurchi bark by intramuscular injection has practically been abandoned as the results were not satisfactory, and the injections caused much pain and an inflammatory reaction

Among other remedies which have been recommended in the treatment of amebiasis and amebic dysentery may be mentioned bismuth subnitrate

the proper surgical measures Perforation of an amebic ulcer into the peritoneal cavity or general peritonitis should be treated surgically in the same manner as are the same complications caused by other conditions but little can be expected from operative measures when these serious accidents occur The treatment of chronic amebic dysentery by such surgical measures as appendicostomy or cecostomy is not recommended and the writer is of the opinion that beneficial results following such operations can be much more easily and surely obtained by proper treatment with amebacidal drugs Fortunately one sees very few cases of severe chronic amebic dysentery in regions where the early recognition of amebiasis is practiced and proper remedial measures are taken to eliminate the amebic infection as early recognition and proper treatment prevent the infection from becoming chronic and also prevent the occurrence of serious complications

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together with the disappearance of tenderness or pain in the hepatic region If the symptoms persist after the completion of the treatment, the condition is either not caused by amebic infection, or suppuration has occurred, and an amebic abscess of the liver is present, which should be treated by surgical measures although some authorities have used emetine injections even after the formation of the abscess with good results, the drug causing encystment of th abscess, if it be small and there is no secondary bacterial infection If the patient s condition is good the emetine treatment should be given a thorough trial before resorting to surgical measures

It is now the concensus of practically all authorities who have had an extensive experience in the treatment of amebic abscess of the liver, that puncture and aspiration of the abscess contents and treatment with emetine hydrochloride result in a much greater percentage of recoveries than the more radical surgical measures as opening the abscess and draining externally with the resection of a rib, if necessary The more radical surgical measures are no longer used unless secondary bacterial infection has occurred or the abscess has perforated into the pleural or peritoneal cavities or into the infrahepatic space, suprahepatic space or extraperitoneally The open operation is also indicated where the abscess cavity refills repeatedly or the symptoms continue after aspiration

The technique of puncture and aspiration in the treatment of amebic abscess of the liver as well as the description of the various methods of open operation, will be found described in standard surgical texts to which the reader is referred

Treatment of Amebic Appendicitis — If symptoms of an acute or chronic appendicitis occur in an individual suffering from intestinal amebiasis, thorough treatment with chiniofon and emetine should be administered before any operative measures upon the appendix are undertaken provided the patient is not in a critical condition

As the writer has stated elsewhere (1934) 'Many patients presenting the typical symptoms of acute appendicitis are promptly relieved by treatment with these drugs and operative procedures for appendicitis in patients having intestinal amebiasis should never be countenanced unless amebicidal drugs have been administered without effect It should be remembered that amebic invasion of the appendix by *Endamœba histolytica* practically always means that the cecum is involved and it has been repeatedly observed that operations upon such patients have led to very serious complications and, not infrequently have been followed by death On the other hand the administration of amebicidal drugs in such cases usually results in the disappearance of the acute symptoms and in the recovery of the patient

The *treatment of other complications* of amebiasis, as amebic abscess of the lungs brain or other organs is essentially surgical but the effect of emetine should be ascertained or the drug should be administered in conjunction with

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CHAPTER XXXIV

THE RELAPSING FEVERS

By JOHN L TODD

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Synonyms —Relapsing fever remittent fever famine fever recurrent typhus tick fever bilious typhoid spirillum fever

In the relapsing fevers fever is characteristically intermittent (see chart) Relapsing fevers are caused by spirochetes Infection by spirochetes is usually carried by lice or ticks The relapsing fevers vary slightly in symptoms and in causation These variations are so slight that it is better to describe the relapsing fevers as one disease caused by Spirochaeta recurrentis

Distribution

Relapsing fever may occur in all parts of the world where men live in verminous surroundings Relapsing fever is characteristically seen wherever human beings are crowded together under unsanitary conditions because the lice and ticks which transmit the disease then increase Relapsing fever has destroyed armies The disease is endemic among the squalid populations of large cities in India and Central Europe

Lice and ticks are often carried on the bodies or in the belongings of

emigrants from endemic areas It is for this reason that when relapsing fever occurs outside of an endemic area it usually appears in ships or along lines of travel

Relapsing fever occurs in Europe now less frequently than when standards of living were not so high It is seen occasionally in Ireland Scotland Norway and Denmark Each year many cases occur in Russia Poland, the Balkan States and Turkey The disease is well known in Greece and in Egypt It is endemic in many places in Northern, Eastern and Central Africa and in Asia Minor It is constantly present in Persia, Indo China and Manchuria In North America cases are occasionally seen usually in immigrants Relapsing fever exists in Mexico Central America and in parts of South America

Etiology

General[1, 2]

Obermeyer found spirochaeta recurrentis in the blood of a relapsing fever patient in 1868 In India Carter showed that men could be given the disease by the inoculation of spirochete containing blood It can be transmitted in the same way to monkeys mice rats and other laboratory animals

Ross and Milne found spirochetes in the blood of persons suffering from African tick fever a form of relapsing fever In the same year (1904) Dutton and Todd[3] confirmed that observation They showed that the organisms are transmitted by a tick ornithodoros moubata and that ticks hatched from eggs laid by an infected parent are also infected During his investigation of the disease Dutton contracted it and died Mackie (1907) with Sergent and Nicolle (1912) showed that relapsing fever is also transmitted by lice The offspring of infected lice are infective

A small number of spirochetes may infect a human being Spirochetes in blood or other material will make their way into the body through the smallest break in the skin They penetrate uninjured mucous membranes and possibly even unbroken epidermis Accidental infection in laboratories and autopsy rooms has often occurred

The observation that relapsing fever prevails among those who live in verminous quarters suggests that the bites of ticks bedbugs lice and fleas may transmit the disease from infected to uninfected persons Living spirochetes can be found in ticks lice bedbugs and mosquitoes for many days after they have ingested infected blood

Lice transmit the parasites not by their bites but through the contamination of scratches with infective material from their bodies It is possible

that infection occasionally may be carried by bedbugs and fleas possibly even by mosquitoes but it is of rare occurrence

Ticks do infect by their bites they also carry the disease in another way In feeding the tick (ornithodoros moubata) fixes its mouth parts in the skin of its host and fills itself with blood While feeding the tick passes anal excretion and clear fluid exudes from its coxal glands The openings of these glands are placed just behind the first leg on each side of the tick s body Anal excretion and coxal fluid mix and surround the tick and the wound which it has made The tick feeds for several minutes During this time the living spirochetes which are present in the coxal fluid of an infected tick may enter and infect the host upon which the tick is feeding

Peculiarities in the incidence of the disease are explained by its method of transmission It is most prevalent in the winter when poor people wash less and crowd together for warmth Boys are le s cleanly than girls in some epidemics boys suffer more Doctors and nurses who care for relapsing fever patients in hospital wards rarely contract the disease orderlies who prepare patients for admission to the wards often do so The patients are cleansed from vermin when they are in the wards the orderlies do the cleansing

The Causal Organism

Morphology and Development—*Spirochaeta recurrentis* the cause of relapsing fever is one of a large and indefinite group of organisms Some spirochetes are free living others are parasitic Some of the parasitic spirochetes produce disease others seem to be harmless Parasitic spirochetes of many varieties are found in the bodies and in all parts of the alimentary canal of living beings ranging from animals to insects in many parts of the world

Little is known of the parasitic spirochetes that do not cause disease still les is known of those that are not parasitic Many parasitic spirochetes are pathogenic Spirochetes cause diseases of poultry horses and sheep Others have been found to cause disease in guinea pigs and in a species of monkey

Some of the spirochetes parasitic in man cause generalized disease others are local in their effects or harmless The spirochetes commonly found about the mouth throat and genitals usually cause no ill effect but sometimes they are associated with severe phagadenic ulcerations of these parts Spirochetes are always found in the foul ulcers often seen in the tropics on any part of the body Spirochetes have been found in urethritis and in dysentery their etiological connection with these conditions is uncertain Spirochetes cause a specific well defined bronchitis The best known of the generalized diseases produced in man by spirochetes are the

relapsing fevers Others are epidemic jaundice and the recurring fevers which sometimes follow the bites of rats and of cats

The classification of spirochetiform organisms is in an unsettled state[1] and their biological position is uncertain They are usually held to be neither bacteria nor protozoa they are usually placed in an intermediate position

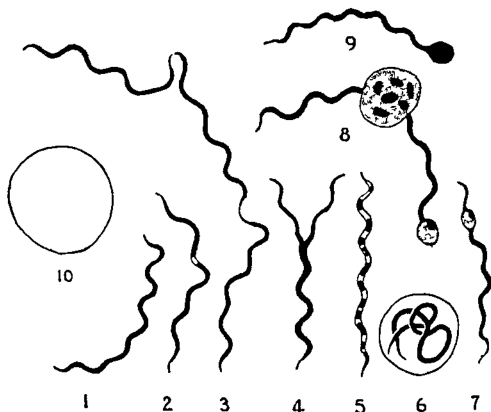


Fig 1 —Diagrammatic Representations of *Spirochaeta recurrentis*

1 —The spirochete as usually seen in the circulating blood
2 —The spirochete showing unstained area
3 —A long spirochete about to divide into three by transverse divisions at the thin places
4 —A spirochete dividing longitudinally a form rarely seen
5 —A spirochete in which the chromatin has become granular
6 —An encysted spirochete
7 and 9 —Spirochetes with lateral and terminal swellings
8 —A spirochete associated with a clump of granules Such appearances have been described repeatedly but a spirochete has never been seen to develop from a granule
10 —A red blood cell for comparison

as protista In this article the term "spirochete" is applied to the organisms causing relapsing fevers They are unicellular filiform parasites They have neither flagella nor undulating membrane and they are dissolved by a ten per cent solution of saponin

Spirochaeta recurrentis is a thread like organism (Fig 1–1) In cross section its body is not circular but flattened[6] It usually measures from 12 microns to 36 microns in length Its average length is about 20 microns Forms as short as 6 microns and as long as 55 microns have been seen The breadth of the spirochete varies it usually measures about 0 3 microns in width At the ends the spirochete tapers to a fine point The body of the spirochete is flexible and is disposed in a number of waves When the waves are numerous the spirochete seems to form a spiral thread hence its name But careful observation of a living spirochete shows that the waves of the spirochete lie in one plane and do not form a spiral The number and amplitude of the waves depend largely upon the manner in which the preparation is made

Living spirochetes are in active motion They move with either end foremost Their motions are of different sorts there is a lashing movement of the whole parasite the waves of the body move along the spirochete and the organism may revolve about its longitudinal axis By reason of their great flexibility and motility spirochetes pass in unchanged form through Berkfeld filters which hold back bacteria [1]

Spirochetes usually occur singly Often two or more are joined together by their ends (Fig 1–3) Sometimes they clump together either in formless masses or in parallel strand like tresses In the blood spirochetes are usually free Sometimes they are attached usually by one end to a red or a white cell All of these things can be seen in a freshly made coverslip preparation of blood

Spirochaeta recurrentis has a thin outer skin or periplast and a central core The periplast is stained pink by Romanowsky s and similar stains The core takes a purple color resembling that taken by chromatin Usually the core stains evenly but not infrequently there is an unstained spot near the junction of a central and terminal third of the organism (Fig 1–2) The periplast extends to form the tapered point of the spirochete for about one micron beyond the core This effilated extension of the periplast has been described in error as a terminal flagellum There are no lateral flagella These things can all be seen in specimens prepared for diagnostic purposes and stained by modifications of Romanowsky s method By special methods appearances have been seen which suggest that a rudimentary undulating membrane or crest may run spirally along the bodies of some spirochetes that an axial filament may run from end to end of the body and that there may be contractile fibers or myonemes in the periplast

In the blood spirochetes usually divide by transverse division They do so by separating at the thinned area apparently consisting only of periplast by which two spirochetes are often united (Fig 1–3) Longitudinal division is less common but it also occurs (Fig 1–4) Spirochetes which are

relapsing fevers Others are epidemic jaundice and the recurring fevers which sometimes follow the bites of rats and of cats

The classification of spirochetiform organisms is in an unsettled state[1] and their biological position is uncertain They are usually held to be neither bacteria nor protozoa they are usually placed in an intermediate position

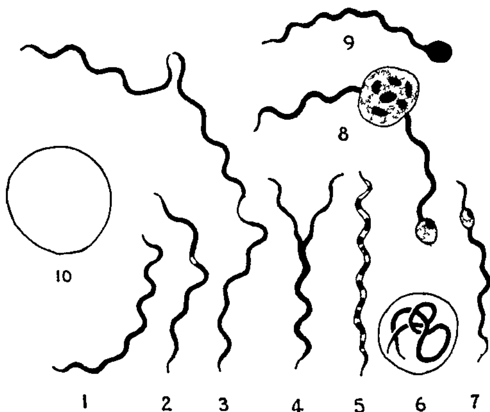


FIG 1 —Diagrammatic Representations of *Spirochaeta recurrentis*

1 —The spirochete as usually seen in the circulating blood
2 —The spirochete showing unstained area
3 —A long spirochete about to divide into three by transverse divisions at the thin places
4 —A spirochete dividing longitudinally a form rarely seen
5 —A spirochete in which the chromatin has become granular
6 —An encysted spirochete
7 and 9 —Spirochetes with lateral and terminal swellings
8 —A spirochete associated with a clump of granules Such appearances have been described repeatedly but a spirochete has never been seen to develop from a granule
10 —A red blood cell for comparison

as protista In this article the term spirochete" is applied to the organisms causing relapsing fevers They are unicellular filiform parasites They have neither flagella nor undulating membrane and they are dissolved by a ten per cent solution of saponin

(8 microns) and normal spirochetes in the preparations developed from these elongated granules is uncertain But their staining their general appearance and the presence of intermediate forms suggested it This observation justified a suggestion (Dutton and Todd 1905–1907[7]) that spirochetes undergo development in ticks The suggestion has been supported by Leishman (1909)[8 9] and by other (Balfour Fantham[10] and Hindle) it is also supported by apparent development of a similar nature in several allied organisms Absolute proof of a developmental process depends upon observation of its occurrence in living organisms No one has seen a granule grow to a comma form and a comma form develop into a spirochete Until that is done the existence of a granular stage in the development of spirochetes will remain in doubt

It has been asserted that the granules associated by some with spirochetal development grow and multiply Leishman believes that a development of spirochetes by granules occurs only under favorable conditions of humidity and temperature (28 C) Others state that temperatures of 38°C and higher may make ticks non infective It is by the continuous observation of living organisms kept under favorable conditions that a decision on these questions may be reached It is probable that the study with dark field illumination of material from infected vermin and from cultures will be fruitful

Spirochetes ingested with infected blood find their way from the alimentary canal to all parts of a tick s body Spirochetes of all sorts with the granules produced by them may be present anywhere in an infected tick and in its eggs Wolbach[11] showed that spirochetes were especially found in the tick s connective tissues They occur less frequently in the coxal and salivary glands and in the cells of the alimentary canal and Malpighian tubules Since spirochetes may make their way to any part of a tick s body it follows that they may be present in any of the tick s excretions or secretions as they are in the fluid from the coxal glands[12] Infection occurs whenever spirochetes contained in a tick s excreta or secretions pass through the epidermis of a susceptible host

It has been suggested that as in malaria the recurring attacks of relapsing fever may be associated with a definite stage in the development of a causative organism During the fever the spirochetes are numerous In the intervals as in malaria the parasites disappear but an exhaustive search may be successful in finding isolated spirochetes in the finger s blood and experimental animals may be infected by the inoculation of considerable quantities of blood At the end of an attack many of the spirochetes die and are ingested by phagocytic cells In preparations made at that time apparently healthy spirochetes are seen within endothelial cells in the liver spleen and elsewhere Whether these apparently healthy organisms are

about to divide transversely are longer than usual those about to divide longitudinally are broader These facts in themselves produce considerable variation in the morphology of the spirochetes on a single slide

The chromatinic core may be broken up into rods or granules of varying sizes (Fig 1–5) Large chromatinic granules are sometimes attached to the end[6] or at the side of a spirochete (Fig 1–7) occasionally the end of a spirochete is enlarged to form a club like swelling (Fig 1–9)

Spirochetes are sometimes tightly coiled to form a skein (Fig 1–6) Such organisms may occur in the peripheral blood They are common in smears from the liver spleen and other organs Sometimes they are surrounded by a finely staining area which suggests that they are embedded in a matrix The chromatin of coiled spirochetes is often but not always fragmented The reason for the coiling is unknown it has been suggested that coiled spirochetes may be in a resting stage Coiled spirochetes are most numerou in preparations made just before the crisis of an attack

Obviously degenerating spirochetes of all sorts are often seen within endothelial cells of the liver and other organs and within phagocytes circulating in the blood Rarely is a spirochete seen within a red cell In a preparation made with material from the alimentary canal of a tick which has fed some days previously on infected blood many spirochetes are seen Some of them are normal some of them are slender others broad Some are short others long The chromatin of some is unbroken in others it is fragmented Some have terminal or lateral swellings or attached granules Some of the spirochetes are tightly coiled many of these have about them the thinly stained area which gives them the appearance of being enclosed in a cyst like matrix (Fig 1–8) The chromatin of spirochetes thus encysted may be so fragmented that all resemblance to a normal coiled spirochete is lost Some of these altered spirochetes are certainly degenerative forms It is quite possible that some of them are developmental

The nature of the chromatinic granules produced by spirochetes has been much discussed Some believe that they are degenerative others state that a granular stage occurs in the developmental cycle of spirochetes The granules produced by spirochetes are of two sorts large granules extruded from terminal or lateral swellings and small ones produced by fragmentation of the chromatin

The formation of small chromatinic granules from a spirochete was first observed in fixed and stained preparations of material from infected ticks In these preparations were forms representing all the stages of a development of spirochetes from granules There were free and encysted spirochetes the chromatin in some of these was fragmented into granules Free granules identical with those seen in the spirochetes occurred Some granules were elongated That the comma shaped bodies and the short

(Phthirus pubis) all carry the disease Human lice exist in all parts of the world Throughout tropical Africa the usual carrier of the disease is a tick Ornithodoros moubata Other ticks carry the disease in Somaliland and Abyssinia Ornithodoros savignyi and in Persia Argas persicus and Ornithodoros tholozani The last named tick occurs and carries the disease in India In Mexico relapsing fever is carried by Ornithodoros talaje and Ornithodoros turicata Infection by spirochetes passes from generation to generation of lice and ticks Ticks remain infected for at least three generations In an endemic area one in every four lice was found to be infected In another area from thirty per cent to fifty per cent or more of the ticks (Ornithodoros moubata) contained spirochetes The morphology life history and habits of ticks lice mosquitoes bedbugs and fleas and the means by which they are destroyed and avoided are described in text books of tropical medicine and of medical entomology

Pathology

The body is usually jaundiced There may be petechial hemorrhages in the skin beneath the mucosa of the mouth and beneath the serosa of various organs Occasionally there may be hemorrhages into stomach and bowel Ecchymoses in thickened and edematous meninges are sometimes confluent In cases where death has followed massive infection there is intense congestion of minute vessels in the brain and cord Manson and Thornton[14] suggest that coma and death in such cases may be due not only to toxemia but to actual occlusion of vessels by tangled masses of spirochetes

Striking is the enlargement of the spleen and liver All organs are hyperemic The spleen is much congested it is soft and is sometimes almost fluid The marrow of long bones may be red Cloudy swelling of the organs is often marked There is frequently fatty degeneration of the heart liver and kidneys especially in rapidly fatal toxic cases Spirochetes rapidly disappear and can only be found in preparations made within a few hours after death In smears or sections spirochetes are found free or within endothelial cells in every part of the body They occur in the cells of lymphatic glands of spleen pulp in the bone marrow and sometimes in renal epithelium

Symptoms

The symptoms observed in cases during a single epidemic may vary greatly It is especially so in endemic areas where many of those attacked have acquired partial immunity through preceding infections In those who

resting, are developing or are about to be destroyed is unknown A rise of fever at the commencement of an attack is then associated with an increase in the number of spirochetes at the end of an attack spirochetes disappear from the blood and many of them are destroyed Two explanations of the disappearance of spirochetes have been proposed One suggests that the spirochetes disappear for reasons connected with the life cycle of the parasite the other suggests that the spirochetes are driven from the blood by the accumulation and action of spirochaeticidal bodies elaborated by the host

Cultivation —Spirochetes live for several hours at room temperature in blood or other material, taken from an infected host They live for forty days if the material be kept at from 2° to 4°C They may be cultivated for an indefinite period by methods based upon those elaborated by Noguchi [4] Spirochetes grow best at 37°C They are most numerous and vigorous about the eighth day

Classification of Relapsing Fever Spirochetes —The relapsing fevers occurring in different parts of the world differ slightly from one another There are differences in the morphology of the causative spirochetes and in the symptoms of the diseases which the organisms produce in man and laboratory animals and hosts which have acquired immunity to one spirochete may be susceptible to another None of these factors has specific value strains of spirochetes showing great differences in morphology and pathogenicity may be derived from a single source and animals immune to one of these strains may be susceptible to infection by another None of these factors is of sufficient importance to justify a differentiation between the relapsing fevers since all these fevers are due to parasites of similar morphology have a similar course and react in a similar manner to drugs There is no practical value in describing several relapsing fevers when the cause symptoms treatment and prophylaxis of all are practically identical It is more useful to treat the relapsing fevers as one disease which may present local modifications

The Vectors

Relapsing fever may be transmitted by any agent which introduces infected material into a susceptible host It is conceivable that the organism may be so transmitted by coitus by the bites of infected animals by the bites of infected leeches fish mosquitoes and fleas as well as by the bites or contamination of ticks and lice Infection has been mechanically transmitted by bedbugs which carried the spirochetes on mouth parts polluted with infected blood Usually relapsing fever is carried by lice or ticks Body lice (Pediculus corporis) head lice (Pediculus capitis) and crab lice

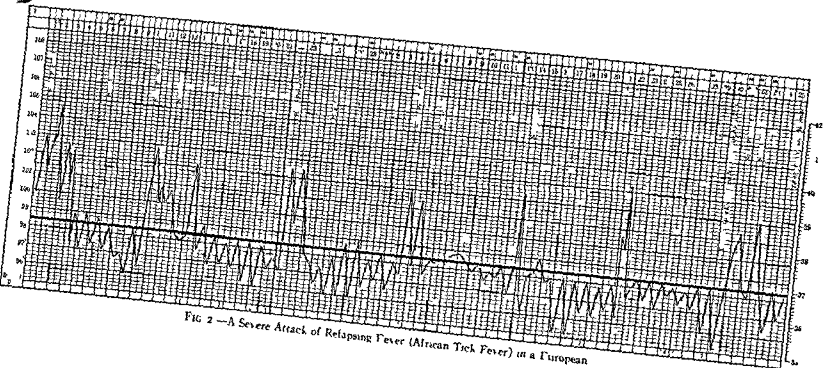


FIG 2 —A Severe Attack of Relapsing Fever (African Tick Fever) in a European

have already had relapsing fever the disease may be entirely atypical and limited to a single abortive rise in temperature The incubation period intervening between the infecting contact with tick or louse and the commencement of an attack is from two to twelve days the first attack usually commences in about seven days after an accidental infection in laboratory or autopsy room Indefinite prodromata such as headache, general malaise and lassitude may be present for a day or two before the definite commencement of the first attack

The onset of the first attack is characteristically sudden Pain in the head muscles back and especially of the long bones—shins—may be great There may be a definite rigor The temperature rises rapidly to 103°F or more (Fig 2) temperatures of 106°F and higher have been recorded With the fever the pulse increases to 115 to the minute, or more The skin is flushed and tender There is thirst There may be nausea and vomiting may be an early symptom The tongue is coated and ordinarily the appetite is gone Constipation or diarrhea may be present or absent Prostration is great Fever continues with a slight morning fall for from four days to a week At the end of the attack the temperature falls rapidly accompanied by profuse perspiration to normal or subnormal

After an attack the temperature remains normal or subnormal Though he may be weak the patient feels wonderfully well and is certain that he is cured But in from four to eighteen days ordinarily eight after the crisis a second attack commences There may be from three to six or more attacks with intervening afebrile periods before the disease comes to an end (Fig 2) The symptoms are the same in each attack but ordinarily they become progressively less severe When there are many attacks the final one though spirochetes are present in the blood may produce only a rise to normal of a subnormal temperature[14] The attacks vary in number duration periodicity and severity In the European form of the disease there are ordinarily but two attacks there may be five In the African form of the disease there are often from three to seven attacks in one case there were eleven There are fatal fulminating cases in which the temperature remains high and there is no relapse In other cases the attacks last for only a day or two and the rise in temperature is negligible

As the disease progresses the skin becomes yellowish and there may be skin eruptions ranging from a fine rash to rose spots or maculae There may be petechiae in the mouth Liver spleen and heart may be enlarged Pain and tenderness of the liver and spleen may be distressing the spleen has ruptured spontaneously Myocarditis is a grave complication Death especially in weak and elderly persons usually results from heart failure at a crisis Herpetic eruptions hiccough and epistaxis are sometimes severe

the phenomena of anaphylaxis and complement fixation may be demonstrated in the usual manner but at present serological methods have little value in the prevention treatment and diagnosis of relapsing fever

DIAGNOSIS

Definite diagnosis is made by demonstrating the presence of spirochetes It is usually easy to find them in preparations of blood The examination of a fresh unstained coverslip preparation of blood from the finger or ear is usually sufficient The preparation should be a thin one It should be examined with an oil immersion lens and with a light that is not too intense Attention is first drawn to the spirochetes by their movement for that reason preparations should be examined as soon as possible after they are made since the movements soon become slowed In preparations examined during hot weather at temperatures approaching that of the blood there is often active motion in pseudopodia from white cells and in fragments of red cells Care prevents any possibility of these being mistaken for spirochetes

If it is inconvenient to examine fresh preparations or if spirochetes are not found in them stained blood slides should be searched The most convenient method of doing so is to prepare and examine a thick film A large drop of blood is placed on a slide and smeared over an area about one centimeter in width The blood is allowed to dry and is then dehemoglobinized by placing it in water After drying it is fixed in absolute alcohol The dehemoglobinization and fixation may be done in one operation by adding one drop of hydrochloric acid to each five cubic centimeters of the alcohol The slide is then dried and stained Almost any nuclear stain will do A modification of Romanowsky s method is usually used because it also stains malarial parasites which may be present The modification recommended by Christopher and Stephens gives good results as do the stains of Leishman Wright Giemsa and Tribondeau If Romanowsky s stain is not available excellent preparations may be obtained with gentian violet or with carbol fuchsin In a well prepared thick film all the hemoglobin is removed and the red cells are unstained All that is seen are the nuclei of the white cells possibly the outlines of a few basophilic red cells the blood platelets and a little fibrinous debris Spirochetes and other parasites that may be present are conspicuous It is sometimes convenient to examine for spirochetes by coloring the background of the slide instead of the spirochetes In doing so a drop of blood is mixed with an opaque fluid such as India ink A smear of the mixture is made on the slide It is allowed to dry and is then ready for examination Spirochetes are seen as unstained refractive threads against a dark background

The urine has the characteristics usually observed in fevers it is often albuminous and may contain casts Hemorrhagic nephritis has occurred

In some epidemics eye complications are not uncommon Iritis iridocyclitis retinitis and conjunctivitis occur photophobia may be intense and there may be temporary blindness

Nervous symptoms are sometimes marked Mental derangement may range from dull confusion to active mania All the signs of meningitis may be present Any of the peripheral nerves may be paralyzed Paralysis may appear suddenly and may persist for many months, but recovery is gradual and complete The paralysis is probably an expression of toxic neuritis The sensation of affected parts is impaired Aphasia, facial paralysis hemiplegia and paraplegia with incontinence of feces and urine have been recorded Epilepsy has occurred In some epidemics bronchitis and pneumonia have been grave complications

Spirochetes can be found in the blood before an attack commences During the attack they are present in increasing numbers there are usually from ten to fifteen thousand per cubic millimeter but often they are more numerous than the red cells Generally speaking the more severe the attack the more numerous the spirochetes They are said to be less numerous in African than in other relapsing fevers

In uncomplicated relapsing fever there is little change in the blood Its coagulability is lessened Red cells and hemoglobin are diminished Autoagglutination of the red cells is often well marked There is a slight increase of the white cells especially at the height of an attack a decrease of eosinophils has been described

Relapsing fever may be complicated by any of the diseases existing in the area where it appears Old infections especially malaria seem to be aroused by an attack of relapsing fever Pregnant women usually abort and deliver a still born child spirochetes can pass through the placenta and infect the fetus in utero

Immunity

An attack of relapsing fever confers immunity but the extent of that immunity varies Individuals have been attacked twice in a single winter In endemic areas those who are constantly subjected to the bites of infective ticks and lice do not develop clinical evidence of infection while strangers succumb to a typical attack of the disease It is probable that immunity under such circumstances is produced and maintained by constant reinfection The immunity which follows an untreated attack of relapsing fever does not result when an attack has been cut short by treatment with salvarsan Lysis agglutination precipitation of spirochetes and

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fever plague typhus trench fever have each in many cases been associated with relapsing fever For these reasons the establishment of a definite diagnosis of relapsing fever by the discovery of spirochetes in the blood is not a reason for omitting any part of an exhaustive clinical examination by which the existence of complicating disease may be discovered

The unusual severity of some of the symptoms associated with relapsing fever may lead to its being mistaken for other diseases For example severe and disabling pains in muscles and joints may suggest rheumatism pain of the long bones may suggest osteomyelitis headache and other signs of meningeal symptoms may suggest cerebrospinal meningitis

Prognosis

In robust persons untreated relapsing fever runs its course and all but about two per cent recover If patients are well nursed and well treated recovery is prompt and complete and the death rate is negligible In adverse circumstances the mortality may be high Death rates of from sixty per cent to eighty per cent have been recorded in epidemics among half *starved populations which received neither nursing nor treatment*

Treatment

Before the discovery of salvarsan the treatment of relapsing fever was entirely symptomatic Symptoms are still treated as they arise High temperature is reduced by baths and sponging Pains and aches are relieved by phenacetin aspirin or morphin Nutrition and the smooth working of the alimentary system are maintained by careful dieting and the employment of laxatives A weakened heart is supported and collapse is combated by the employment of adrenalin caffein and camphor When the appetite returns in convalescence overeating is a danger During the attacks all patients are kept in bed elderly and weakened persons are rigidly confined to bed during the whole course of the disease and they more than others must be warned against the danger of sudden exertion especially at a crisis

Salvarsan and allied drugs *are specifics in the treatment of relapsing* fever Since salvarsan cures the disease by destroying spirochetes its use is rarely contraindicated It should be given even when there is albumin in the urine The drug acts best intravenously When it is administered subcutaneously or intramuscularly its action is uncertain and slow The drug may be exhibited at any time in the disease but the spirochetes are

In examining a stained preparation for spirochetes, a mechanical stage should always be used in order that the preparation may be systematically and thoroughly viewed. At least ten minutes should be spent in examining the preparation before it is assumed that it does not contain spirochetes.

Stained preparations are usually examined with an oil immersion lens by a strong light. In the examination of specimens prepared by special methods for the study of detailed structure the highest magnifications are necessary and it is of advantage to employ monochromatic light obtained either by means of a prism or by the use of a screen of malachite green glass. If stained preparations are examined by dark field illumination the spirochetes may be recognized with a magnification of only 125 diameters (⅓ inch or 8 mm objective no 4 eye piece).

If spirochetes cannot be found they may be proved to be present by inoculating not less than twenty five cubic centimeters of blood into the peritoneal cavity of a young white rat. The rat's blood must be examined twice daily for ten days without finding spirochetes before it can be assumed to be uninfected.

If circumstances prevent a direct diagnosis by demonstrating the presence of spirochetes the clinical course of the disease may justify a diagnosis of relapsing fever. The typical relapsing character of the temperature in relapsing fever is very characteristic. Nevertheless it is to be remembered that the attacks of fever in this disease are often abortive and irregular and that the course of the fever may be entirely atypical when relapsing fever is complicated by intercurrent infections.

Differential Diagnosis

The blood invariably should be examined at the commencement of every fever in areas where relapsing fever is likely to occur. There are many cases on record where lack of examination resulting in late recognition of the nature of the disease has caused improper and unsatisfactory treatment. When malaria and relapsing fever coexist the diseases are often mistaken for one another unless careful microscopic examination of the blood is a routine practice. The coincidence that the temperature fell at the crisis of an attack in relapsing fever just after a dose of quinin had been given has often been erroneously accepted as a therapeutic proof of the malarial nature of the disease. The microscope makes such an error impossible.

The method by which relapsing fever is transmitted proves that those suffering from it have lived under unsanitary conditions. Consequently many relapsing fever patients suffer from double infections. The frequency with which relapsing fever is complicated by ordinary infections and inflammations has already been referred to. Malaria trypanosomiasis pappataci

or petrol and by mercurial preparations such as the ointment of ammoniated mercury In very lousy and unkempt persons it is sometimes advisable to cut off all hair Those who cleanse relapsing fever patients before admission to hospital wards should wear louse proof clothing Ordinarily only lice and ticks transmit relapsing fever Nevertheless the bites of all pests should be avoided

Ornithodoros moubata which usually transmits relapsing fever in Africa is often found about places where natives live or have lived For this reason old camping places and natives houses are to be avoided in districts where relapsing fever exists They are to be avoided even though they have been long unused Ticks can live and maintain their infectivity for years without food It is often better for a caravan of unimmune persons to spend a night camping in the bush than to risk sleeping in a tick infested village These ticks hide during the day in sand filled cracks of the floors of native houses At night they come out to feed They dislike light and a night light deters them from moving Ornithodoros savignyi bites by day as well as by night Ticks are unable to climb smooth surfaces so bedsteads with smooth legs give some protection to those who sleep in them

Relapsing fever may be carried by young ticks small enough to get through the meshes of an ordinary mosquito net nevertheless a well constructed mosquito net gives much protection since all but the smallest ticks are unable to pass it Ticks are often carried for long distances in bedding of travelers For that reason all bedding should be aired and well shaken daily in districts where ticks occur

No means of destroying ornithodoros is known beyond catching them by hand or burning houses infested with them

It is not known how spirochetes survive from one epidemic of relapsing fever to the next They might do so in three ways in man by occasional atypical cases of relapsing fever or as harmless tolerated parasites in animals such as monkeys or rats or in invertebrate hosts such as lice and ticks Animals of several species can be infected with spirochaeta recurrentis but no certain instance of natural infection in an animal has been recorded Therefore it is as yet unnecessary to attack an animal reservoir of infection from which the invertebrate transmittors of relapsing fever might derive spirochetes

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more completely destroyed if the injection is given at the commencement of an attack while the temperature is rising A full dose given at the commencement of the first attack often accomplishes a complete cure If a relapse occurs after one dose a second usually suffices to complete a cure It is believed that spirochetes are less able to survive medication if salvarsan is given in full doses for this reason it is inadvisable to give the drug in small doses Salvarsan in a dose of 0 01 gram for each kilogram of the patient s body weight usually brings the temperature to normal and drives all parasites from the peripheral circulation A dose of one half of this amount has a similar effect but a relapse is likely to occur In some epidemics a small dose of salvarsan (0 3 gram) has been sufficient Neosalvarsan in the same doses as salvarsan and the allied drugs galyl and ludyl (0 3 to 0 5 gram), given intravenously like salvarsan are equally efficacious and are said to cause less reaction and to be less disturbing to the patient Arsalyt given intravenously in a dose of 0 5 gram is said to give as good results as does salvarsan The severe reaction which sometimes follows within one or two hours after the injection of these drugs is possibly due to the liberation of toxins through the sudden destruction of large numbers of spirochetes During the reaction the temperature may rise and there may be vomiting

Many other drugs such as atoxyl arrhenal potassium iodide and quinin have been advocated in the treatment of relapsing fever The value of these as of serum therapy is negligible

Prophylaxis

When a disease is caused by one parasite the spirochete and transmitted by a second the louse or tick preventive measures may be directed both against the causative parasite and its vector Relapsing fever is easily controlled because there are efficient means for destroying the parasite and for destroying or avoiding its carriers

The salvarsan group of drugs destroys the spirochetes of relapsing fever so easily and completely that the disease can scarcely remain endemic in an area where these drugs are freely and properly employed An additional advantage gained by the early treatment of infected persons is that the chances of vermin being infected from them are lessened

Patients should be carefully protected and cleansed from vermin in order that vermin may not become infected by feeding upon them or go from them to uninfected persons Lice leave a fevered patient Lice are easily destroyed in clothing and bedding by steam Persons are cleansed and kept free from lice by the free use of soap and water combs kerosene

CHAPTER XXXV

THE TRYPANOSOMIASES OF MAN

By DAVID WEINMAN

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14 MANSON J K and THORNTON L H D Jour Roy Army Med Corps London 1919 XXXIII, 97 and 193

PART II

Definition and Characteristics

African trypanosomiasis is an infectious non contagious human disease which is progressive usually fatal if untreated and caused by *T gambiense* or *T rhodesiense* Clinically it is marked by an initial lesion often unperceived fever particularly at the outset generalized enlargement of the lymph nodes skin rashes cardiovascular disturbances edema and a variety of neurological manifestations of central origin which become more marked as the disease progresses

History

In the early accounts of trypanosomiasis in Africa the significant observations have come quite as much from reports on animal as from reports on the human trypanosomiases This interconnection may be understood readily The vectors often are identical or closely related and the trypanosomes themselves distinguishable at times only with the greatest difficulty so that the two often have had similar epidemiological features

Taken together the trypanosomiases human and animal have influenced the development of Central Africa very greatly Human populations have been decimated and in certain regions more than decimated and animal husbandry and animal transport rendered difficult or impossible The net retarding effect of these circumstances is not easy to overevaluate In a very literal sense the trypanosomiases not only have a history but within their field of action have determined the course of history to a degree which few diseases have done Many features of life in Central Africa today have been so determined and only thus can be understood

As early as Agatharchides who flourished about 150 B C it was believed according to Hegh[4] that animal husbandry might prove impossible in Africa since at certain seasons the cattle were killed by the poisoned sting of flies and it is a somewhat dreary observation to note that approximately 2 000 years later Livingstone was recording a very similar comment There is reason to believe that several attempted conquests of Central Africa failed at least in part because of trypanosomiasis The Mohammedan push from the Sudan toward the south was stopped because the ponies of the cavalry died presumably from try

Introduction

The human trypanosomiases fall naturally into two large groups, African trypanosomiasis, described in Part I, caused by *Trypanosoma gambiense* and *Trypanosoma rhodesiense*, and Chagas' disease, described in Part II predominantly South American, provoked by *Trypanosoma (Schizotrypanum) cruzi* There are records of infection by what are primarily animal trypanosomes which have strayed into a human host since these are of no practical medical import, they will not be discussed further (for details see Brumpt[3])

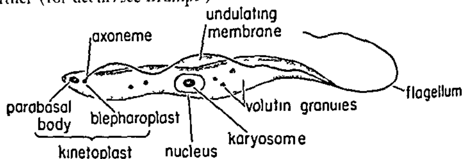


FIG 1 Diagram of a *Trypanosoma* (Mackie Worth Hunter)

The trypanosomes infecting man are flagellated micro-organisms of simple structure details being shown in Figure 1 They are transmitted by blood sucking insects each species of trypanosome undergoing a developmental cycle within the appropriate insect, at the end of which infective forms are produced

Other species are parasitic in animals and the group is perhaps of as great importance in veterinary as in human medicine An abbreviated account of the mammalian trypanosomes is given by Hoare and Coutelen[1], a detailed description will be found in Wenyon Trypanosomes are classified in the phylum *Mastigophora*, family *Trypanosomidae*

PART I

AFRICAN TRYPANOSOMIASIS

Synonyms — African sleeping sickness maladie du sommeil Schlafkrankheit somnolenza doenca do sono and formerly negro lethargy human tsetse fly disease mal de Loanda , etc

from Johnston who speaks of the appalling growth of African diseases which followed the colonizers and states The opening up of the Continent has carried the terrible sleeping sickness over much of Uganda German East Africa and British Central Africa It is of interest that Stanley in his expedition to relieve Emin Pasha in 1888 may have been an unwitting agent for the dispersal of trypanosomiasis from West to East Africa[7 11]

Once the disease did arrive in East Africa it flourished in particularly virulent form notably in the region of the great lakes, where in one area for example a population of 300 000 was reduced by two thirds in a period of eight years[8 11]

The bases for the scientific study of the disease were laid in the nineteenth century The genus *Glossina* was created in 1830 and the term tsetse introduced in 1850 by the hunter Gordon Cumming[9] Meanwhile some knowledge of the trypanosomes had been acquired Gruby created the genus *Trypanosoma* in 1843 in 1873 Lewis observed trypanosome infections in mammals and a trypanosome disease of horses, was reported in 1880 by Evans Bruce related trypanosomes to tsetse flies in 1895 by showing that nagana the anciently known fly-conveyed cattle disease of Africa could be transmitted by *Glossina* and was caused at least in part by what is now known as *Trypanosoma brucei*[8 11]

The modern period begins with the observation of motile structures in the blood of a febrile patient in Gambia by Forde in 1901[13] Dutton later examined the same case recognized the parasites and proposed the name *Trypanosoma gambiense*[14] Linkage of this non malarial fever with negro lethargy followed when Castellani with the aid of Bruce and others isolated trypanosomes from the cerebrospinal fluid in 20 of 34 cases and also from the blood of some of the same patients[1] Some authors apparently following Manson[17] state that Nepveu in 1891 was the first to observe trypanosomes in man However consultation of Nepveu s descriptions and illustrations does not permit of the identification of trypanosomes[11 1] The second generally accepted species *T rhodesiense* was described in 1910 by Stephens and Fantham[16]

Although glossina was rather generally believed to be the vector after 1903 the capital point the extrinsic cycle was not established until 1908 when Kleine showed that during a period of some weeks in glossina the trypanosomes underwent a developmental cycle at the end of which the fly became infective and remained so for a long period * This contrasted strongly with the previously held view of a short lived mechan

panosomiasis (Johnston in Hegh[6]) Likewise this was true for the Portuguese expeditions of the sixteenth and seventeenth centuries, loss of horses was a major cause of their failure (Johnston)

The earliest human case known at present is that of an Arab king in the western Sudan who died in 1373, after suffering from a progressive disease said to be common in the region which terminated after two years of somnolence[8, 9] In the European literature the Portuguese Alexio da Abreu as early as 1623 referred to the disease as the 'mal de Loanda'[10]

The growth of trade and in particular the slave trade, led to an interest in this disease in the eighteenth century and we find it mentioned by several of the English travelers[11] Winterbottom, who was in Sierra Leone about 1792 was perhaps the most interesting of the group He described the characteristic enlarged cervical nodes and stated that slave traders considered these "small glandular tumors" a symptom indicating a disposition to lethargy and "never buy such slaves or get quit of them as soon as they observe such appearances" His own opinion was that the nodes depended upon 'accidental circumstances' and not the disease[1] History ignored his judgment and honored his eyesight by eponymizing such swollen nodes as *Winterbottom's sign* The disease was disseminated with slaves despite the acumen of slave traders and was observed in the Americas as early as 1808 by Moreau de Jonnes[8]

The great impetus to the study of the disease came with the seizure of the African continent by the European powers Previously regarded as it has been put as an exporting area whose chief commodity was human beings from about 1870 onwards Africa became increasingly subject to development with a corresponding growth of trade betterment of communications and movement of peoples So far as the disease was concerned this had two effects not only were the colonizers brought into intimate contact with this condition which was depleting the available manpower and occasionally themselves but also the disease was spread to portions of the continent where it found particularly favorable conditions and appeared in epidemics of such severity that it threatened large areas with depopulation

Before 1880 according to Scott[8] the disease was unknown in East Africa Livingstone who followed the course of the Zambesi from Central to East Africa considered the tsetse harmless to man and emphasizes the point in view of its noxious action on cattle "A most remarkable feature in the bite of the tsetse is its perfect harmlessness in man"[8] By 1900 the situation had changed entirely and there can be little dissent

Prevalence and Importance

Comprehensive figures are not obtainable and recent data are particularly incomplete In 1936 140 000 new cases were found in the course of nearly 7 000 000 examinations , an incidence of about 2 per cent in those examined Since the population of tropical Africa is estimated at 65 000 000 these surveys *investigated only a portion of the* possible cases That the number detected may not accurately indicate the total is suggested for example, by the figures available for Nigeria 5 681 cases detected and treated in 1943 of 265 000 examined[4] whereas the total number of infected persons has been estimated at more than 1 000 000 in the northern provinces alone[2]

More accurate estimates can be made for certain regions such as the Belgian Congo or French West Africa where 25 to 30 per cent or more of the population is examined annually In French West Africa there were over 35 000 known living cases in 1941 with over 31 000 cases found that year[6], in the Belgian Congo 28 300 cases were encountered in 1945 about one third of these new cases and during the period 19 6 1945 more than 365 000 new cases had been discovered[10] In the Gold Coast the disease accounted for 7 3 per cent of the deaths in the hospitals in 1941 ranking behind only tuberculosis and diseases of early infancy[8] In East Africa in the past some of the most severe epidemics have occurred Tanganyika Territory reported 785 cases for 1946 and a total of 23 995 for the period 192 through 1946 of which 11 500 or about half have died or will die of the disease a serious loss to an underpopulated country[2] Less than 500 new cases were reported from Uganda in 1940 but in 1941 1943 an epidemic occurred in the Lake Victoria region which by 1943 involved 500 persons[4] For additional information see Willcocks and associates[3] and the map (Fig 2)

The effort organization and expense which has gone into sleeping sickness work was and is enormous In French West Africa 4 414 533 persons were examined in 1941[6], in the Belgian Congo this figure exceeded 5 000 000 for 1936 for 1945 it was 3 300 000 and the total for the period 19 6 1945 is more than 70 000 000 examinations The treatment campaigns and anti tsetse work of the last thirty years have attenuated the effects and modified the distribution of the disease but no final solution to the problem has been reached nor is it even in sight For example in the Belgian Congo where as noted treatment campaigns have been pushed with great vigor for some time the ratio of new cases to the

ical process of transmission but was confirmed rapidly by Bruce and others[9] working with *T gambiense* in *G palpalis*

Effective medication became available in 1905, when Thomas introduced atoxyl an organic quinquevalent arsenical compound first synthesized by Bechamp in 1863 This was widely used until Jacobs and Heidelberger[1] produced tryparsamide, another quinquevalent organic arsenical which Pearce and Brown found [23] to have pronounced action in experimental *T gambiense* infections Used in the field with great success[1] tryparsamide has markedly improved the prognosis and remains one of the two drugs of choice The other is antrypol or Bayer 205, a non metallic symmetrical urea of complex structure, which is extremely active in the early stage The formula of Bayer 205 was kept secret apparently for both political and commercial reasons but this attempt at exclusive control came to an abrupt end when Fourneau at the Pasteur Institute of Paris synthesized the apparently identical and equally active Fourneau 309 and, publishing the formula, made the drug generally available

Little or no mention has been made of the views of the natives concerning trypanosomiasis In the study of any endemic disease certain opinions of the local population have proved to be very well based and not infrequently to indicate which lines of research might be fruitful It may not be without interest therefore to note some of the correct ideas and the practices of the Africans concerning trypanosomiasis They were aware that the cervical swellings were associated with the lethargy (see for example Winterbottom as already referred to) and in certain regions practiced excision of the "neck-stones" as a means of arresting its progress a practice still current in Liberia among the Buzzi The role of the tsetse as the conveyor of animal disease was firmly believed in at the time of Livingstone and Cumming (1850 1860) In regard to human sleeping sickness Bruce's attention was drawn to a belief of the natives of French Guinea who attributed it to the bite of a fly[8] Measures against the fly were instituted also and according to Balfour natives of the Sudan devised a tsetse trap consisting of a gourd baited with blood The first organized attempt by man to eliminate tsetse flies and nagana was undertaken as Swynnerton (in Strong Bequaert and Cleveland[4]) states by a Zulu chieftain in Portuguese East Africa from 1861 1889 It was decided to render the district fit for cattle by settling it closely and driving out the game it is said that, where the game was actually driven out, the tsetse disappeared

of the areas under infestation cattle cannot be kept in a vast proportion of them sleeping sickness still takes its toll of the human population despite the high efficacy of modern drugs and a huge expenditure on staff and organization treatment and segregation in the various countries concerned

Maintenance of present achievements will require unceasing attention any more permanent solution to the trypanosomiasis problem requires improved methods of treatment and control

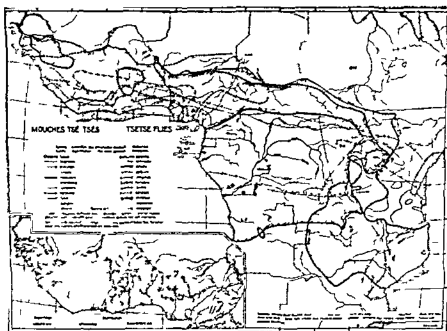


FIG 3 Distribution of *Glossina* in Africa (Deutschman)

GEOGRAPHICAL DISTRIBUTION

Human trypanosomiasis is endemic only in tropical Africa between approximately 15 north of the Equator and 20 south latitude It extends in the west from Dakar in Senegal to Benguela in Angola attaining long stretches of the coast and some islands in the Gulf of Guinea

population examined declined from 1 . per cent in 1926 to 0 27 per cent in 1938 [9] Despite this notable achievement, it has been impossible to lower this figure since then, the situation appearing stabilized for the past seven years Meanwhile there has been an alarming increase in the number of cases resistant to treatment Similarly, tsetse control, applied with success in many regions has not prevented the fly from advancing in other areas Thus in Tanganyika from 1929-1936 2,000 square miles were lost to *Glossina* (Swynnerton, in survey of Wilcocks and associates [8]) and in 1938 a seven year program of research was laid out with

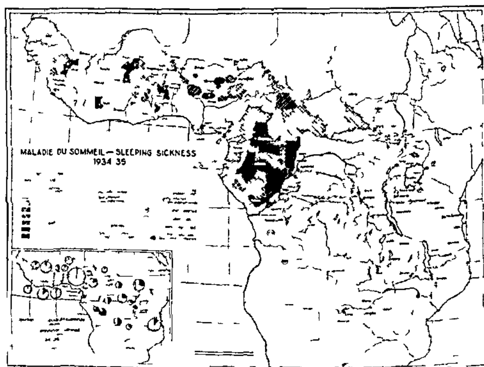


Fig 2 African Trypanosomiasis Geographical Distribution (Deutschman)

£243 000 allotted to it G *morsitans* is said to be reoccupying territory where it has been unknown since 1900 and in Beuchuanaland human cases are now being seen[31]

It seems evident that despite all advances made, trypanosomiasis remains a major African problem Swynnerton[32] well summarizes this the greater part of tropical Africa amounting to some 4½ million square miles is under infestation by the tsetse in the greater parts

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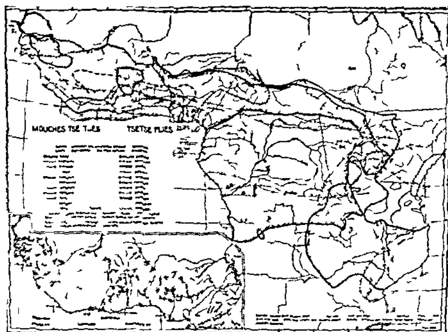


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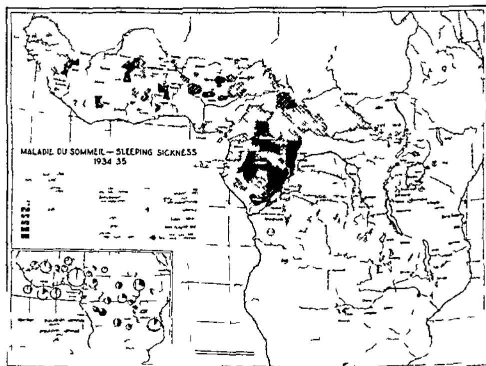


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weeks the entire episode may be terminated Varying from the type described are lesions with minute vesicles over the summit those which are painful due to the hindrance to swelling because of the area involved i e angle of the jaw and those which are waxen in appearance and surrounded by a white ring[3] The initial lesion is sometimes termed a Graffian chancre in this author's view a double misnomer (1) the lesion bears no resemblance to hard or soft chancre in the majority of cases (2) although Graf[34] drew attention to a somewhat neglected phenomenon this neglect occurred despite the teachings of Manson at least twenty years earlier (see (41) and Lane (in 35))

Trypanosomes are found in the local lesion before they appear in the blood The organisms have been detected even before swelling has taken place and it is not rare to find them about the fourth or fifth day in fluid obtained by puncture or deep scarification The initial lesion occurs in both *T gambiense* and *T rhodesiense* infections and in the latter apparently in the majority of patients Corson observed it in 9 of 30 volunteers[36] Fairbairn and Burtt in 91 per cent of their 206 experimentally infected volunteers[37] but Duke in only 7 of 17 cases[38] This variation may depend among other things on the number of trypanosomes inoculated[37] Although it has been suggested that the reaction is to the fly bite rather than to the trypanosomes it did not follow the bite of uninfected flies[39] furthermore infective blood injected subcutaneously gives rise to the progressive local swelling[40]

Onset and Invasion

The local initial lesion often is unperceived and the disease then appears to start with constitutional symptoms These may be either pronounced and definite or the condition may become established so gradually that no precise starting point is evident The latter type is said to be more common in Africans whereas the abrupt onset is observed frequently in Europeans

The fever which develops at this time often becomes more pronounced than during any other phase of the disease It begins not uncommonly with a sharp rigor from one to three weeks after the infective bite After increasing throughout a few days it reaches a maximum of 103 to 104 F persists for about a week then subsides usually gradually Respiration rates are increased and correspond with

e.g. Fernando Po. In the east it reaches from the southern Sudan to Southern Rhodesia and Bechuanaland. Within this very large area the distribution is irregular, absent in some portions, the disease is particularly prevalent in others, notably along the large rivers and their affluents. Reference to the map (Fig. 2) on a previous page will give details. For such supplementary information as is available since the end of the war see Wilcocks and associates.[8] Liberia has been partially surveyed by Veatch. The most infected area found was in the north in the portion extending between Sierra Leone and French Guinea, the infection rate for the Western Province ran from 1 to 3 per cent. in 1943-1944, a figure attained after some years of treatment in the area.

T. rhodesiense occurs in East Africa and is found in Uganda, Tanganyika, Nyasaland, Southeast Central Africa and the Southern Sudan.[3, 4] As will be seen later, strains of *T. gambiense*, which are indistinguishable from it, occur in Nigeria and probably elsewhere.

The distribution of tsetse flies is somewhat more extensive than that of the disease, and from areas which contain potentially good vectors no cases have been reported (compare distribution of the disease and of the tsetse, Figs. 2 and 3). *Glossina tachinoides* has been reported from the Arabian peninsula in the vicinity of Aden but a number of authors consider the locality erroneous; no reports of cases from the area have been encountered.

Clinical Description

The Initial Lesion

The bite of an uninfected tsetse is neither extremely painful nor pruritic and subsides fairly promptly. Conversely, the bite which inoculates human trypanosomes is followed often by a marked local reaction. The puncture wound forms the center of an area, which becomes swollen and inflamed, the reaction progressing throughout two or three days before reaching the acme. At the peak of development the area is distinctly reddened, circular in outline with a diameter of about 6 to 8 centimeters, raised about 1.5 centimeters above the adjacent surface and frequently has a darker spot in the center. It is sensitive to pressure rather than painful and gives a fluid sensation below a thickened skin. There is often regional adenopathy with tenderness and enlargement and moderate fever. The lesion persists at full development for a few days, then regresses, usually leaving no trace, so that at the end of about two

are very long and the intervals of fever brief or perhaps lacking altogether

The pulse which is accelerated when fever is present remains fast during afebrile periods This feature, described as characteristic is variable regularly observed in acute T rhodesiense infections it may be absent in mild T gambiense cases

Asthenia with a disinclination to exertion is common Sexual impotence often appears early in males and may be the somewhat misleading initial symptom for which medical attention is solicited If an analogous state occurs in females it is not reported but menstrual disorders are not seen until terminally[4] Pregnancy may be initiated throughout the course of the disease but in the later stages spontaneous abortion may take place and if born alive the offspring may die in infancy[4] or present abnormalities (e g hydrocephalus) at birth[13]

The most constant distinctive and consequently valuable sign at this early stage is the enlargement of the lymph nodes The first affected is the regional node draining the initial lesion later there is generalization cervical nodes (Winterbottom's sign) and epitrochlear axillary and inguinal groups being frequently involved The enlargement usually is moderate the nodes reaching 1 5 to 2 0 centimeters in length and raising the overlying skin only slightly above the adjacent surface (Fig 4)

The nodes are freely movable and are firm and elastic to the touch They may be painful while enlarging particularly in the axillary region but once fully formed are not sensitive except to applied pressure Puncture of such nodes in the early stages frequently discovers trypanosomes and is an important means of diagnosis Later the nodes become smaller harder and fibrous and trypanosomes are more difficult to isolate from them Nodes do not suppurate unless secondarily infected

Skin rashes sometimes termed trypanides are common in light skinned persons but either do not occur or cannot be seen in negroes They appear on the trunk more often than on the extremities and most typically are rounded forming either portions of a circle or having joined arc of circle contours The margin usually is of a distinct red or red-violet color the center colorless Curved linear forms and solid patches of varying sizes are seen also These rashes usually do not itch disappear without desquamation and leave no trace Their duration is variable and after disappearing they may recur

An anemia of moderate degree usually is present and often difficult to attribute to its true cause in malaria infected helminth bearing patients Undoubtedly however, uncomplicated trypanosomiasis does

the temperature but the pulse often is not proportionally accelerated Characteristic of the fever are marked remittences or even intermittences and after subsidence recurrences at irregular intervals The recurrences are in general neither so pronounced nor so prolonged as during the first attack Finally this 'primary fever" merges with that characteristic of the declared disease

Trypanosomes usually are present in the blood at the time the fever commences or shortly thereafter, and in 206 experimental fly transmissions to volunteers 85 per cent had trypanosomes in the blood between *the seventh and the fourteenth day*[7] *Since the organisms* are said to be more common, when the fever is more pronounced, blood examination preferentially is made during febrile exacerbations

Quite frequently the fever is absent or goes unnoticed, and a period of months or years may pass before symptoms attract attention At other times the disease begins with a major symptom and patients apparently healthy the day before have been brought to the hospital in coma to find that they were suffering from cerebral trypanosomiasis

Usually the onset and invasion is as described although varying in degree and after subsidence of the initial fever so readily attributed to malaria, a period of weeks months or even years elapses before other signs or symptoms either cause the patient to seek treatment or permit detection during examination

Signs and Symptoms

Pain is often the presenting symptom and while varied in site and intensity some variety is very rarely lacking Headache is extremely common it is persistent and usually frontal or referred to the vertex Pains in the back and articulations muscular cramps and neuralgic pains of various sorts are seen in various combinations

Disturbances in the sleep pattern occur early Most often *nocturnal* insomnia is combined with diurnal somnolence and at times the patient more conscious of his insomnia may request soporifics to combat his sleeplessness at night

Fever, whose outstanding characteristic is its irregularity usually is present at some time Most often moderate and not exceeding 101 F it persists for a day or two with a *morning remission between* and then disappears to recur a week or two later In certain patients particularly it seems, in those with a mild form of the disease, the afebrile intervals

The cardiovascular system is involved probably more often than has been recognized particularly in *T rhodesiense* infections The pulse is abnormally rapid and often there is a tachycardia of about 100 which persists during afebrile periods The arterial blood pressure is said to be low generally[31], but detailed studies of the heart appear to have been neglected perhaps quite wrongly so in view of the cardiac lesions found post mortem

Eye lesions of various sorts have been described interstitial keratitis iritis iridocyclitis as well as changes in the retina These are said to vary in frequency and intensity being particularly marked in certain epidemics Ridley[4] has cast some doubt upon the whole matter having found that in the Gold Coast many of the ocular manifestations could be attributed to a concomitant *Onchocerca volvulus* infection which had passed undiagnosed because of the lack of slit lamp examinations He states that intra ocular inflammation due to trypanosomes within the tissues is very rare follow infections of the meninges and central nervous system and then resemble the disturbances seen in other forms of lymphocytic meningo encephalitis papilledema and more rarely ophthalmoplegias Argyll Robertson pupil and nystagmus It still remains to be shown that throughout the trypanosomiasis belt *Onchocerca* is everywhere equally accountable also that trypanosomiasis alone may not provoke the lesions cited Data from animal experiments may not be immediately applicable but they do show that in a suitable host trypanosomal infection alone may set up some of the eye conditions noted in man

Symptoms thus far described often are classified as being of the pre cerebral stage They are followed by more marked neurological manifestations this subsequent period being termed the cerebral stage This terminology based on major symptoms rather than spinal fluid examinations is used often but seems misleading and as it may tend to give an incorrect picture of the pathogenesis and corresponding therapeutic problems involved objectionable

In fact invasion of the nervous system often takes place early it can occur within a month of onset and precisely because the nervous system is involved already be incurable To term this the precerebral stage even although classical nervous symptoms are lacking is to misconstrue what is actually taking place Furthermore it can hardly be maintained that certain symptoms usually placed in the precerebral period have anything but a cerebral origin (tremors deep hyperesthesia, persistent headache etc)

induce anemia, as the very regular occurrence of lowered red cell counts in infected animals indicates[44] The spleen and liver are enlarged, but likewise the etiology is not always single



Fig 4 African Trypanosomiasis Enlarged cervical lymph nodes "Winterbottom's sign" (Friedheim)

Edema is a frequent and often an early symptom, occurring particularly about the eyes ankles and in the lower extremities The slight puffiness of the face is one of the elements causing the peculiar facial expression of this disease Somewhat later it may give a false impression of slight obesity in contrast to the actual progressive emaciation taking place

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The data are clearest in *T rhodesiense* infections Keevill[16], in 53 consecutive cases, obtained 13 histories of less than one month of illness, and all had abnormal spinal fluids, trypanosomes were observed with counts as low as 5 or 10 cells, in another series of 94 consecutive cases 10 gave histories of illness under 21 days, and none had a normal cell count[1] Fairbairn[18] has found that possibly as high as 25 per cent of patients with a history of less than one month duration may be incurable, these are the patients with a high spinal fluid protein It may be objected that too much reliance is placed upon the patient's cooperation in determining the length of illness However animal experiments, in which the length of infection is precisely known, are in full agreement[19, 20, 21]

In *T gambiense* infections the mildness of the infection makes it difficult to approximate its duration However it is certain that in many patients even with few or no symptoms of any kind, and which would thus be classified as in the precerebral stage, the central nervous system is involved already Marquiessac and Y Bertrand[3] selected new patients with few or no symptoms and in their pooled results more than one third (34 and 46 per cent) of 639 new cases had abnormal cerebrospinal fluids Veatch[2] found 72 per cent of his patients had abnormal fluids in the stage which was symptomatologically the invasion period In general such changes do not have as unfavorable a prognostic significance as is reported for *T rhodesiense* cases

The progress of the infection is very variable In Liberia many of the author's patients had migrated from endemic areas to a fly free region where for many months they performed hard manual labor had no complaints and were detected in the course of routine examinations Elsewhere and notably in *T rhodesiense* regions in four to six weeks the cases already may be far advanced

If untreated the disease inevitably progresses, although spontaneous regression of certain signs and symptoms facial paralysis, swollen cervical nodes may occur as Gelfand[4] has noted Possibly, exception should be made for the few reports of spontaneous cures However the nervous symptoms almost invariably become more marked Lesions being widely disseminated in the brain and cord symptoms vary correspondingly Tremors of the hand fingers or of the tongue are extremely common and often are seen quite early They may be fine are less often coarse but are not of the intention type Parkinsonian rigidity is absent except in very rare cases and these of uncertain etiology

Romberg's sign is observed frequently Clonus of the patella more rarely of the ankle, is not uncommon The tendon reflexes in general

are abnormal increased at first diminished or abolished later There are abnormalities in sensation and *Kerandel's sign*", so named, for the physician who suffering from sleeping sickness himself left a graphic description of this symptom is highly characteristic although not very frequent It consists in a deep hyperesthesia of delayed onset such that the turning of a key in a stiff lock may give rise to a pain which is scarcely bearable

Various types of pareses or paralyses occur hemiplegias or paraplegias sometimes with incontinence paralysis involving isolated muscles or muscle groups which when accompanied by paresthetic symptoms resemble alcoholic neuritis (Guillain and Seze[a]) When the conditions persist long enough permanent rigidities and contractures may result Accompanying these symptoms are various functional difficulties the walking becomes difficult and speech thick or even unintelligible The mentality is affected reflection becomes difficult and there may be abrupt changes of character Epileptiform convulsions are not rare

Various psychical disturbances have been observed and the disease has declared itself with an attack of acute mania Other patients suffer from hysteria or delusions the majority sooner or later if the disease lasts long enough have periods of stupor

The patient may now present the classical picture of sleeping sickness He is dull and apathetic he comprehends poorly he is disinclined to exertion and frequently goes to sleep even in the direct sunlight and this sleepiness so masters him that he fails to awake even for the necessities of food and cleanliness (Fig 5)

Meanwhile the symptoms of the earlier period have undergone certain modifications The fever becomes much less prominent it is less high when it is present and there may be apyretic intervals of several weeks duration or longer particularly if the patient is under treatment The lymph nodes tend as time goes on to shrink and become fibrous if punctured the needle often comes away with little or no cells and fluid Trypanosomes which were earlier found with relative ease either in the blood or the nodes now become scantier

At this point successful therapy is much more difficult but if the trypanosomes are not resistant there is often a remarkable and rapid response although complete restoration to normal may no longer be possible Untreated or with poor response to therapy the symptoms become more marked if unhospitalized and exposed the patient may slowly starve unable to fend for himself his feet can become riddled with jigger fleas or fly maggots if he does receive care only adequate

The data are clearest in *T rhodesiense* infections Keevill[46], in 53 consecutive cases, obtained 13 histories of less than one month of illness and all had abnormal spinal fluids, trypanosomes were observed with counts as low as 5 or 10 cells, in another series of 94 consecutive cases 10 gave histories of illness under 21 days, and none had a normal cell count[47] Fairbairn[48] has found that possibly as high as 25 per cent of patients with a history of less than one month duration may be incurable, these are the patients with a high spinal fluid protein It may be objected that too much reliance is placed upon the patient s cooperation in determining the length of illness However, animal experiments, in which the length of infection is precisely known are in full agreement[49,50,51]

In *T gambiense* infections the mildness of the infection makes it difficult to approximate its duration However it is certain that in many patients even with few or no symptoms of any kind, and which would thus be classified as in the precerebral stage the central nervous system is involved already Marquiessac and Y Bertrand[3] selected new patients with few or no symptoms and in their pooled results more than one third (34 and 46 per cent) of 639 new cases had abnormal cerebrospinal fluids Veatch[52] found 72 per cent of his patients had abnormal fluids in the stage which was symptomatologically the invasion period In general such changes do not have as unfavorable a prognostic significance as is reported for *T rhodesiense* cases

The progress of the infection is very variable In Liberia many of the author s patients had migrated from endemic areas to a fly free region where for many months they performed hard manual labor, had no complaints and were detected in the course of routine examinations Elsewhere and notably in *T rhodesiense* regions, in four to six weeks the cases already may be far advanced

If untreated the disease inevitably progresses although spontaneous regression of certain signs and symptoms, facial paralysis, swollen cervical nodes may occur as Gelfand[4] has noted Possibly, exception should be made for the few reports of spontaneous cures However, the nervous symptoms almost invariably become more marked Lesions being widely disseminated in the brain and cord symptoms vary correspondingly Tremors of the hand fingers or of the tongue are extremely common and often are seen quite early They may be fine, are less often coarse, but are not of the intention type Parkinsonian rigidity is absent except in very rare cases and these of uncertain etiology

Romberg's sign is observed frequently Clonus of the patella, more rarely of the ankle, is not uncommon The tendon reflexes in general

up to 95 per cent of the total and far from being early cases were actually mild but prolonged some to fifteen years or more. As regards the spinal fluid some 50 per cent of these cases may show minor changes.

The moderate cases are those which seek treatment[8] and accordingly may form a portion of the cases of a hospital or dispensary which is disproportionate to their incidence in the country as a whole. The early stages have well marked symptoms and signs of nervous involvement make their appearance without too much delay and increase in severity until death.

The *acute type* usually the exception in *T. gambiense* infections is common in *T. rhodesiense* outbreaks on which the following description is chiefly based. Within four to six weeks of illness the patient may be in an advanced state as was noted in the outbreak from 1940 1945 in Uganda.[9] Nervous symptoms are inconspicuous or lacking although the cerebrospinal fluid is markedly abnormal in at least 25 per cent of the patients. In the most marked cases the onset is sudden with sharp fever the pyrexia is sustained without remission emaciation is rapid and pronounced there are no serious cerebral symptoms and if untreated the cases die in two to three months. This is very similar to the toxic form which Lester[7] observed in *T. gambiense* areas. Another rarer type has an acute onset as described but accompanied by severe nervous disturbance. These cases may without warning fall into a semi coma or following a few days of headache collapse and be found to have marked paresis of the legs.[10]

Attention has been called by Buchanan[11] to the frequency of cardiac abnormalities in *T. rhodesiense* cases. Those lasting much over one month show instability of the pulse and persistent tachycardia. In cases lasting over three months from [illegible]0 to 70 per cent show additional abnormalities consisting of weakened sounds evidence of dilatation and alteration of rhythm.

Parkinsonian type cases have been found in the French Sudan by Sice and associates and are said to be more frequent than formerly. Although encountered in patients infected with trypanosomes the etiology does not seem altogether clear.

Finally it should be mentioned that a clinico anatomical classification is used sometimes with individualization of such forms as the hemiplegic paraplegic paralytic cerebral medullary cerebellar epileptic maniac etc.

nursing will prevent emaciation of extreme degree Finally death ensues, sometimes caused by terminal secondary infections

Clinical Types

There are acute and chronic forms and the prevalent type often varies from one region to another The mild disease has a protracted evolution over several to many years during much of which time the





Fig 5 Photographs taken at an interval of a few minutes illustrating uncontrolled sleep The meal unfinished the patient has fallen asleep food dribbling from the mouth and running over the chest The dull staring expression and slightly swollen face are characteristic (Todd)

patient is not incapacitated and may even perform hard manual labor Such cases often are discovered during surveys or while being examined for malaria yaws gonorrhea etc and are most common in *T gambiense* areas In Nigeria this was the common type in field surveys, constituting

up to 95 per cent of the total and, far from being early cases were actually mild but prolonged some to fifteen years or more[5] As regards the spinal fluid some 50 per cent of these cases may show minor changes[7]

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Diagnosis

Of greatest importance are the procedures leading to establishment of the diagnosis and those which by analysis of the spinal fluid indicate involvement of the central nervous system

Diagnostic Procedures

Examination of the Blood — In fresh blood trypanosomes, which are two to four times as long as a red cell are very conspicuous structures, which with their active lashing movements flail the red cells to and fro and draw attention at once They should be stained for verification and then have the appearance illustrated in Fig 6 Any of the current modifications of the Romanowsky technique is satisfactory, i e methods of Giemsa, Wright Leishman etc, Field's stain also answers well When trypanosomes are abundant thin films are satisfactory and are preferable for morphological detail, when scanty, the thick drop technique is advantageous and should be used always in surveys

When these methods fail differential centrifugation may succeed since it utilizes much larger quantities of blood The technique is as follows Withdraw 5 to 10 c c of blood and mix with an anticoagulant such as heparin or sodium citrate Centrifuge three times, the first time until almost all the red cells are thrown down and discard the red sediment 1 000 r p m for 3 minutes usually is satisfactory, centrifuge the remainder a second time to sediment the remaining red cells, again at 1 000 r p m for 3 minutes once more discard the sediment and centrifuge the supernatant portion this time at 1 500 r p m for 20 minutes It is advisable not to use much higher speeds or the trypanosomes may become injured and unrecognizable Discard the supernatant fluid and examine a drop of sediment directly under the microscope if negative make a thick drop and stain appropriately Also blood may be laked and then centrifuged Prates[60] recommends 20 per cent methyl alcohol in distilled water which is said to hemolyze the erythrocytes and fix the trypanosomes The proportions recommended are 1 0 c c of blood to 10 c c of the hemolyzing mixture

Inoculation of the Blood — Animal inoculation has the advantage of using large quantities of blood In Africa laboratory-reared animals kept in insect proof quarters should be used, the employment of trapped animals apparently free from infection can give uncertain results Mice

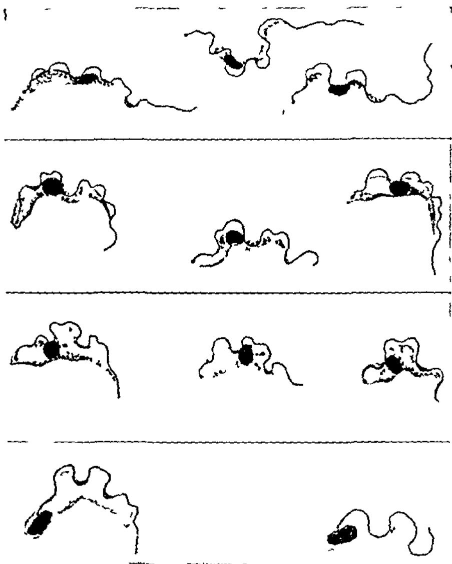


Fig 6 *Trypanosoma gambiense* and *Trypanosoma rhodesiense* Illustrating the polymorphism observed *prior to repeated animal passage* Upper three rows — *T gambiense* showing variations in length breadth and absence of free flagellum on the shortest forms All these types occur in *T rhodesiense* infections Lowest row — Postero nuclear forms of *T rhodesiense* (Bruce)

and guinea pigs usually are employed Mice have the advantage of a short incubation period and a frequently fatal infection, conversely the amount of blood which can be injected is small, so that a number should be inoculated also some strains of trypanosomes do not infect mice readily In guinea pigs larger amounts of blood may be injected, but the disease has a longer incubation period and tends to be more chronic

Preferably both mice and guinea pigs should be used and when possible young animals The injections are made intra abdominally and should be as copious as possible about 0 50 to 1 0 c c for a mouse and 2 0 to 5 0 c c for a guinea pig depending on size Rats and rabbits also are sensitive While rabbits tend to a chronic course the infection is often fairly acute in rats particularly when young animals are used, a possible source of confusion is the spontaneous infection with *Trypanosoma lewisi* Should doubt arise *T lewisi* is morphologically different, it is inoculable to rats and more rarely mice only, runs a spontaneously self limited course is easily cultivable on blood agar (NNN) medium and these cultures are infectious

Blood examinations should be made at least twice weekly from the first through the sixth week At times great difficulty will be found in establishing the strains once established usually they can be carried on without difficulty

Puncture and Examination of the Lymph Nodes — This is an essential examination which giving a high percentage of positives, should never be neglected unless the diagnosis is established by other means Success is more probable before the nodes have become sclerotic Enlarged cervical nodes are chosen unless the enlargement is obviously due to some other cause other nodes may be used, the inguinal nodes probably being the poorest choice A medium caliber rigid needle (about a U S No 19) 2 to 2½ inches long with medium bevel is used The skin is disinfected and the node held firmly from below by the fingers of the left hand which pinch the skin, bring the two skin folds underneath the node raise it to the surface and apply pressure against it The sterile needle is taken by the right hand and inserted through the skin into the node The needle then is rotated and given a few minute to-and fro movements to make the cells and fluid well up into the needle With proper illumination it is possible to see into the shaft and determine whether the puncture has been productive The needle then is withdrawn with a sharp motion a syringe fitted and the contents expelled The drop or two which is obtained may be divided one part examined in the fresh state and the other stained with the thick drop technique

Examination of Spinal Fluid — An examination of this should always be made before and after treatment as a guide to therapy and as a control of its efficacy Puncture is performed in the lumbar region almost universally although Manson Bahr[71] particularly has recommended suboccipital puncture as devoid of risks and less likely to produce headaches About 10 c c fluid should be obtained half in each of two tubes If abundant trypanosomes may be found in the unconcentrated fluid if not found a portion should be put aside for the cell count the remainder centrifuged and the sediment examined

Trypanosomes occur in the fluid with great frequency either when absent from the blood and lymph nodes or conjointly They may be found very early in the disease and particularly in *T rhodesiense* infections where it has been reported that half of the patients with a history of illness of less than three weeks had trypanosomes in the fluid and all had abnormal cell counts[4] Although the organisms may be seen with as few as 5 to 10 cells[16] they are more commonly associated with marked abnormalities of the spinal fluid

Discussion — In the blood the number of trypanosomes fluctuates very widely and there are negative periods when they are apparently absent Preferably examination should be made during pyrexia since there is evidence that peak periods coincide with fever As these peaks may occur at an interval of about a week[6] re examinations performed three and five days later may succeed where the original one failed

The respective merits of blood and lymph node examinations have involved numerous discussions from which one conclusion can be drawn since either may be negative both should be performed Bone marrow punctures often detect trypanosomes[63] sometimes when they are absent from the blood and lymph nodes and even in advanced meningoencephalitic cases[4] Bone marrow puncture is not so frequently positive as the customary methods but can be used when they are negative Likewise the examination of peritoneal or pleural fluid may from time to time be indicated

Other Laboratory Findings — Those which concern the *spinal fluid* are the most important and this realization has developed from the fundamental work of Broden and Rodhain Sice and others The fluid usually clear is opalescent if many cells are present occasionally it is xanthochromic A cell count should be made always for an increase is often the only evidence of abnormality This pleocytosis almost always antedates a rise in the protein and often is observed before trypanosomes are detected In the absence of treatment the count tends

to rise steadily, it may stabilize at 500 to 600 or so or reach 1,000 to 1,800 or more The cells present are chiefly mononuclears, lymphocytes predominate particularly at first, then as the numbers increase, monocytes, plasma cells a few polymorphonuclears and occasionally, the peculiar 'morular cell', actually a Russell body, are found

The cell increase usually precedes the protein rise By the time 30 cells are reached half the fluids will show increased albumin and with 100 cells or more all or nearly all the fluids have abnormally large amounts With treatment the cells decrease first, then the albumin, but it may be very difficult to obtain completely normal values (see Treatment Criteria of Cure) The cellular reaction is almost always the more rapid of the two this lability it has been suggested is due to an underlying anatomical difference, the cells mirroring meningeal inflammation the protein parenchymatous lesions of the brain Data on protein values are given later in the section on Prognosis

The pressure of the fluid usually is low, readings of over 56 mm were reported in only 7 of 118 patients by van den Branden and Appelmans[6] but it may reach 100 mm or more In general the dextrose and chloride contents are decreased and with treatment approach normal values[68]

Tests depending on the presence of globulin (Pandy's, Weichbrodt's) are positive as are the various colloidal reactions Guillain[66] states that the colloidal benzoin test was positive in every one of 6 cases Lange's gold test is considered by some to give the very earliest indication of nervous involvement[6] but in estimating relapses Fairbairn[11] found it a less sensitive indicator than the protein estimation

Examination of the *blood* discloses a moderate anemia, which may be exaggerated by other causes malaria, hookworm, etc The monocytes are moderately elevated and the monocytosis tends to increase somewhat with the progress of the disease The total number of leucocytes fluctuates, with leucocytosis early in the disease leucopoenia later (Sicyro Nieto) The same author reports an increase in platelets and a lowered coagulation time

The *blood chemistry* shows marked protein changes The serum globulin is increased while the albumin is either normal or decreased leading to an inversion of the albumin globulin ratio[9] The blood calcium is low[69] The sedimentation rate is high in some 90 per cent of trypanosomiasis patients and decreases under treatment to reach that of the normal African standard which is above that found elsewhere[71]

Clinical Diagnosis

A patient with a history of fever and of a temporary rash who complains of weakness emaciation, persistent headache and either insomnia sleepiness or both and who is found to have enlarged lymph nodes particularly cervical and to have resided in tropical Africa should be suspected of trypanosomiasis As always once the diagnosis is entertained it is not so difficult to prove or disprove it and no single item is more helpful than the clue of residence in Central Africa Even a temporary stay can suffice and careful questioning may be required to elicit the history of a few days hunting trip Also exposure may have taken place some years prior to the development of symptoms and Pinard and L Brumpt report an exceptional case giving a history of having been outside endemic areas for fifteen years Infants it should be kept in mind, may contract their infection congenitally and have no history of African residence

A detailed comparison with the cosmopolitan nervous diseases which trypanosomiasis may resemble would be too extensive to be entered into here Two nonencephalitic infections require particular consideration in the differential diagnosis malaria and infectious mononucleosis Since malaria is common in tropical Africa it should be anticipated that malaria and trypanosomiasis will coexist in some patients These dual infections will be detected by symptoms unknown or uncommon in malaria and which persist despite an antimalarial therapy which markedly reduces the plasmodial count

Infectious mononucleosis is not often confusing but the mistaken diagnosis has been made and may be adhered to tenaciously because of the fever enlarged lymph nodes mononucleosis and presence of heterophile antibody However buccopharyngeal symptoms are rare or *absent in trypanosomiasis and minor characters of the sheep cell agglutination* will permit of its differentiation[2]

PROGNOSIS

The most important factor is the stage at which treatment is instituted Diagnosed at the stage of the initial lesion and suitably treated very nearly all cases should be readily curable as shown by the many experimental infections of volunteers with *T rhodesiense* described by Corson Fairbairn and others

Past the initial stage, and this includes the vast majority of cases actually dealt with, two factors regulate the prognosis, the sensitivity of the trypanosomes to treatment and the extent to which the central nervous system is involved. In all early infections, i.e. before the trypanosomes are established in the central nervous system, there is a choice of therapy and the prognosis generally is good. Once the trypanosomes can carry on an independent existence in the brain, the principal factor is the sensitivity of the organism to cerebrally active therapy, and at present this signifies sensitivity to tryparsamide. Accordingly the prognosis as to life is good even in fairly advanced *T. gambiense* infections of the usual type but poor in advanced *T. rhodesiense* cases or in those cerebral *T. gambiense* infections which prove to be tryparsamide resistant.

Some precision can be given to these general statements by analysis of the spinal fluid. For prognostic purposes the protein content is widely used. Protein is usually determined either by opacity or by precipitation methods. The two give different values, the opacity readings being 50 to 100 per cent higher according to Hill,[1] who considers the Sicard Cantaloube precipitation method preferable, since less subject to individual variation in making readings than the opacity method as currently used. Normal, determined by precipitation, is 22 milligrams per 100 c.c. or less. Harding accepts 35 milligrams per 100 c.c. (opacity method) in estimating cure rates since yaws alone may produce this amount. While this may be satisfactory for the purpose intended, a figure over 25 milligrams should not be dismissed as normal and thus indicating a postponement of tryparsamide treatment in sleeping sickness patients.

Normal protein usually is taken as 20 to 22 milligrams per 100 c.c. with 25 milligrams as the upper limit. When the figure is below 30 milligrams, a cure can almost always be obtained, from 30 to 40 results are more doubtful, above 40 milligrams *T. rhodesiense* cases are considered late and probably incurable,[4] and this probably also applies to tryparsamide resistant *T. gambiense*. With a sensitive and mild strain of *T. gambiense* it is claimed that recovery still is possible in half the cases with 67 milligrams per 100 c.c. but when 78 milligrams are reached a fatal outcome is inevitable.

It should be emphasized that the quantity of protein shows no invariable correlation with the apparent duration of the disease nor with the symptoms. In less than one month after apparent onset *T. rhodesiense* cases may have a high spinal fluid protein and already be incurable.[1]

and pronouncedly abnormal fluids are seen in patients with inconspicuous symptoms They converse however long standing advanced cerebral cases with normal protein apparently does not occur

The other factor sensitivity to tryparsamide is difficult to gauge and at present usually cannot be predicted van Hoof recommends the following as a rough test for person with blood or lymph node infections Inject one maximum tolerated dose (Or 0 06 gms /kg) of tryparsamide intravenously examine the blood and lymph nodes 48 hours later If trypanosomes are present the strain is tryparsamide resistant if they are absent, no conclusion can be drawn[30, 6]

Pathology

Trypanosomiasis is characterized by a non suppurating lymphocytic and plasma cell infiltration of all the organs and tissues especially of the brain There is no pathognomonic lesion and the perivascular infiltrates of the brain and meninges are characteristic but not distinctive Trypanosomes have been demonstrated throughout the central nervous system but surprisingly enough their identification has been neglected in nearly all pathological studies

The description princeps was made by Mott in a series of papers from 1899 to 1910 the first therefore antedating the discovery of the etiological agent Trypanosomes were demonstrated in the human brain by Stevenson[4] although previously Wolbach and Binger in 1912-1913 had done so in animals Bertrand Bablet and Sice[8] have given a critical review of the literature a propos of two cases studied by modern methods Lesions of the lymph nodes and in prolonged cases of the central nervous system have been most constantly observed, cardiac lesions are present also particularly in *T rhodesiense* cases.

Gross Changes

Emaciation is present in longstanding cases Edema may be observed about the face ankles and occasionally the articulations The lymph nodes are enlarged Fluid often containing trypanosomes may be present in the pleural peritoneal and articular cavities this occurs more often in acute cases or as a terminal phenomenon in mild ones.

The lungs usually show nothing of great interest, perhaps a few minute hemorrhages, whereas the heart may be overly firm or flabby and show areas of hemorrhage and discolored necrotic regions The liver and spleen are moderately enlarged as are the lymph nodes The latter are firm to hard depending on the progress of the infection and may show some hemorrhage on section

In prolonged cases there is pathological change in the brain The meninges may be obviously thickened and adherent opaque or simply edematous maximal changes occur over the convexity and part way down the sides basal meningitis is more rare On incising the arachnoid a considerable quantity of fluid may escape Likewise, an excess of fluid occurs at times in the ventricles resulting in distension The brain sometimes edematous usually shows no marked gross changes although small hemorrhages and areas of softening have been observed

Histology

Nervous System — Sleeping sickness is a meningo myelo-encephalitis with disseminated lesions A perivascular infiltrate is the principal manifestation This is according to Bertrand, Bablet and Sice[80], predominantly plasmocytic and the proportion of plasmocytes is greater than that observed in any other infection These authors find the infiltrates comprised of glial elements, neuroglial and microglial, plasmocytes and monocytes of vascular and meningeal origin and 'morular cells' described in a following paragraph Polymorphonuclears are scanty or absent

These perivascular collections are widespread particularly abundant in the white matter of the brain with the largest collections in the deeper portions, and all levels are involved, cortex central gray nuclei cerebellum medulla Identical collections are found in the meninges and may occur in the viscera (Fig 7a) This infiltrate originates within the Virchow-Robin space i e the continuation of the subarachnoidal space formed by the pia along each blood vessel as it enters the nervous tissue Modern usage terms such collections perivascular although the term so applied was at one time considered incorrect (see Spielmeyer[8])

The morular cell described by Mott[81] frequently is found in these collections and scattered throughout the brain These cells are rounded measure 5 to 15 micra and have a reticulate cytoplasm which gives the cell a peculiar mosaic like appearance (Fig 7a,b) The nucleus usually



FIG 7 African Trypanosomiasis Encephalitis a) Infiltrate predominantly perivascular and scattered "Russell bodies" (Bertrand *et al*) b) "Russell bodies" higher magnification (*ibid*) c) Trypanosomes in brain substance (Stevenson)

is found to one side, stains darkly and may be pyknotic or fragmented The cytoplasm stains with eosin or fuchsin the nucleus with basic stains Morular cells are derived from altered plasma cells, as Mott originally suggested[81] and are now considered to be identical with 'Russell bodies' They are found in other diseases and thus, although having no conclusive value in the microscopic diagnosis, are in sleeping sickness particularly constant and widespread

The blood vessels usually have normal endothelial and subendothelial layers whereas the adventitium is tumefied and very probably furnishes cells to the surrounding collections Mott[83] reported small capillary hemorrhages as a regular finding, other authors find them much less constantly

Parenchymatous lesions are not outstanding and according to Mott[81] are secondary to the vascular changes There are some alterations in nerve cells which appear swollen or atrophied but the figures of irreversible change are usually absent[80] As Mott observed[81], there is no system tract sclerosis in the brain or cord All subsequent workers have emphasized the absence of any disturbance of the cyto architectonics There may be some loss of myelin within the zone of infiltration, this is not constant and when it does occur, the region involved is very small[84, 80]

Almost all histological descriptions fail either to mention trypanosomes or state that they were not seen Yet, when a suitable technique is used they are easily demonstrated and may be abundant (Fig 7c) The present author found the following highly satisfactory Fix in Regaud s solution (3 per cent potassium dichromate 4 parts, formalin 1 part, it is not necessary to neutralize the latter) Section at 5 micra or preferably less and stain with Giemsa s fluid according to Wolbach s technique Schaudinn s fluid is also a satisfactory fixative for subsequent Giemsa staining as Wolbach and Binger showed many years ago[9] Peruzzi[19] found that the trypanosomes stained well with hematoxylin eosin after alcoholic sublimate if his monkey material was fixed within five hours of death

Wolbach and Binger[9] demonstrated trypanosomes in the brains of monkeys within the perivascular lesions in the meninges and in the substance of the brain In human brain tissue Stevenson[85] detected trypanosomes without difficulty The organisms showed a notable tendency to grouping being numerous in some fields and rare in others, in greatest number in the frontal lobe and also present in the pons and medulla Stevenson concluded that the terminal stages of sleeping sickness are

due to an invasion of the brain substance by the trypanosomes, that they arrive in that situation by migration through the vessel walls, and that the perivascular infiltration is connected with this migration

Meningeal lesions are of the type seen in the brain The *infiltrate has* the same topography and the perivascular collections are the same It is often possible to follow the infiltrate along a vessel from the meninges *into the brain substance* The leptomeninges are proliferated and there is proliferation also in the pial sheath which penetrates into the brain with the vessels Apparently the meningeal lesions precede the cerebral ones[85]

In acute cases death may occur before organization of extensive brain lesions whence the relative infrequency with which such lesions are observed in untreated *T rhodesiense* infections[6] Calwell[84] however noted marked perivascular infiltrate in one *T rhodesiense* case where the total duration was apparently under two months also in 14 of 17 more prolonged cases as did Mackie[87] in 2 instances lasting one and five years

Lymph Nodes — In the early stages when the nodes are enlarged there is pronounced multiplication of the reticulo endothelial elements and the sinuses contain numerous macrophages some with ingested white and red cells[83, 81] Trypanosomes may be abundant[89] but there is much variation and the present author has at times found them impossible to demonstrate in nodes known to be positive by previous puncture

There may be some increase in the connective tissue of the capsule with strands passing from it to the center of the node As the disease progresses the fibrosis becomes more marked and thickened bands of connective tissue develop giving the node an alveolar appearance

Heart — Cardiac lesions were observed by the early workers (e g Thomas and Breinl[88]) but despite the experimental findings of Peruzzi[89] they were neglected until Lavier and Leroux[90] and Hawking and Greenfield again called attention to them They occur more frequently in *T rhodesiense* patients The lesions combine inflammation marked by a predominantly mononuclear cell infiltration with a progressive sclerosis The condition is a pancarditis endocardial lesions being the least marked

The myocardium shows a *diffuse and focal infiltration with* a tendency for the infiltrate to lie along vessels and connective tissue septa The muscle fibres are mainly normal but some appear fragmented Again we note the amazing fact that the etiological agent usually is not described Peruzzi[89] however in experimental infections in monkeys noted that the trypanosomes are specially numerous on the surface of

the cardiac fibres and even penetrate into their interior", when favored by cleavage and fragmentation of fibres Typical trypanosomes were found and also a peculiar rounded or oval, non flagellated form (leishmanoid) with large nucleus and a 'blepharoplast", which sometimes could not be demonstrated The latter do not have the significance of the intracellular form in Chagas disease, they are 'accidental relationships with the protoplasm and do not show the phases of an intracellular cyclical evolution typical of other trypanosomes it is a case of manifestation of malignancy which almost always characterizes the trypanosomes of *rhodesiense* type " (Peruzzi[49])

When the evolution is prolonged sclerotic changes become prominent Lavier and Leroux[90] in two such *T gambiense* cases describe bands of connective tissue which in the myocardium start particularly from arteries lace the muscle and give it a septate appearance They also report arteritis of the coronaries and pronounced sclerosis of the epi and endo cardium

Pathological Diagnosis — The situation and constitution of the infiltrates is suggestive but not conclusive As always the diagnosis must be established by demonstration of the etiological agent This seems obvious but neglect of this evidence has been the rule As a result the interpretation of very interesting atypical cases has been uncertain because the etiology is uncertain Also it is well to anticipate the future, the history of the virus encephalitides in Africa is now being written surely it is pointless to neglect a diagnostic aid which may prove invaluable in discrimination It is of interest that early authors laid great emphasis on the frequency with which bacterial infections were observed at autopsy (Castellani[15] Mott[81]) Mott in fact was unwilling to attribute the pathological changes to the trypanosomes alone until animal experiments convinced him that bacteria played no part in their causation Recent authors usually make no mention of examination for bacteria

Pathogenesis

Just how early invasion of the brain substance takes place is unknown, as noted pathological reports usually omit description of the trypanosomes In animals this may take place with a surprising frequency precocity and intensity (author s unpublished experiments), the lesions, however require some time to develop as might be anticipated, and are not seen until some time later In man it is known that trypanosomes

and pleiocytosis may occur in the spinal fluid very early in the course of the disease These events may not be accompanied by symptoms and this is doubtless the ground for the belief formerly held that invasion of the central nervous system takes place only after the disease has evolved through months or years

Once arrived in spinal fluid the trypanosomes may not immediately find a foothold Peruzzi[40] observed in monkeys an early migration of the trypanosomes from the vessels of the choroid plexus into the spinal fluid where he believed they were rapidly killed off if the albumin content were not sufficiently raised In vitro tests with human spinal fluid although only remotely analogous to the conditions in the body favor the view that increased albumin favored survival of the trypanosomes[88]

Whether trypanosomes meet with initial difficulty in establishing themselves in the human nervous system is unknown but such a view affords an explanation of the curious fact that blood sterilization alone sometimes may cure patients in the very earliest stages of cerebral involvement as in the successes reported with antrypol and orsanine (Sice[91]) where the spinal fluid was definitely although only slightly abnormal

The genesis of symptoms is not entirely understood Mott[83] attributed them to the perimeningitis which itself results according to Stevenson[85] from the migration of the trypanosomes through the vessel walls This view then attributes the symptoms to the inflammation and not immediately to the trypanosomes Whether perivascular infiltration adequately explains the lethargy is uncertain Vascular cuffing is a relatively banal lesion and is seen in many types of chronic leptomeningitis[89] Mott himself pointed out how strongly the infiltration around the vessels resembled that seen in general paralysis On the other hand lesions of the centers controlling sleep such as occur in Cruchet von Economo s disease have not been described with any regularity If it be supposed that some trypanosomal toxin provokes the somnolence then the demonstration of the toxin is yet to be made

Etiology

Definition and Description of Trypanosomes

The trypanosomes of interest in relation to African sleeping sickness are *Trypanosoma gambiense* *Trypanosoma rhodesiense* and the mor

phologically indistinguishable parasite of animals, *Trypanosoma brucei*. These three form a distinct group which is often referred to as the polymorphic trypanosomes or from the first member described, the *T. brucei* group. They are distinguished from other trypanosomes by their morphology and by the type of development in glossina which, involving migrations in the digestive tube and salivary apparatus, terminates with the production of infectious metacyclic forms which are inoculated by the bite. *T. brucei* is differentiated from the other two by its inability to infect man. The generic term *Castellanella*, occasionally used in designating these trypanosomes, e.g., Jacono[92] is not generally considered valid.

The general structure is as follows. The body is torpedo shaped, contains a nucleus usually centrally located, a prominent rounded or rod-shaped granule termed the kinetoplast, situated at the posterior end and a variable number of granules scattered throughout the cytoplasm (see Fig. 1).

The kinetoplast is composed of two parts, which usually appear fused: the blepharoplast which probably has a motor function, and the parabasal of uncertain significance and known not to be an essential structure. From the blepharoplast arises a flagellum which runs forward to the anterior end and terminates either there or projects beyond the body as a free flagellum. A short distance from its origin the flagellum leaves the body proper and runs along the peripheral edge of a narrow delicate undulating membrane which thus unites the flagellum to the body. In reaching the anterior end the flagellum winds back and forth; this throws the undulating membrane into folds, the motor effect being to impart a rotatory motion to the propulsive action of the free flagellum.

Two main forms are found, short and stout and long and thin, as well as intermediates, whence the description polymorphic (Fig. 6). Upon blood passage to animals there is, after numerous passages, a pronounced tendency to monomorphism with prevalence of the long forms.

The extreme size range of *T. gambiense* is from 15-33 micra with an average length of 24.3 micra (Bruce[93]). The short forms are stout with an average breadth of [illegible]5 micra and have no free flagellum, i.e., it does not extend beyond the body. The long forms are slender, averaging 1.5 micra in width, and have a free flagellum measuring some 5 micra or more. Many authors distinguish an arbitrarily defined intermediate form usually [illegible]0-[illegible]4 micra long.

The long forms are those which divide in the blood and from them it is believed the short forms are derived (Robertson[94], Wenyon[2]). A

similar belief is held for *T rhodesiense* (Fairbairn and Culwick[6]) It has been suggested (Robertson[4]) that only the short forms infect *Glossina* but subsequent painstaking studies by van Hoof and associates[3] are not confirmatory

The preceding description based on *T gambiense* applies to the whole group members of which cannot be distinguished with certainty on morphological grounds The range of variation includes a certain proportion varying with the strains which will have the nucleus situated in the posterior end near or even posterior to the kinetoplast a particular feature of *T rhodesiense* and *T brucei* (Fig 6) In from 0 5 to 2 0 per cent the parabasal may be absent (Laveran) and altogether rarely anucleate forms occur[3] Certain chemicals cause the parabasal to disappear this effect is inherited and so-called ablepharoplastic strains have been thus produced The scattered granules in the cytoplasm vary in number from strain to strain usually termed volutin granules they have been shown to contain ribonucleic acid which is responsible for their staining reactions (van den Berghe[9])

Reproduction takes place by longitudinal fission Usually the parent gives rise to two daughter trypanosomes in intense infections trypanosomes dividing into three or even more occur There is first a duplication of the kinetoplast then the flagellum splits from the blepharoplast anteriorly to about one third its length this is followed by division of the nucleus (Robertson[4]) and the terminal stages ending in separation of the cytoplasm Within the human body this multiplication by division usually binary is the only type known Six chromosomes have been described in the nucleus[10] but there is disagreement in regard to their number and disposition during division Sexual forms fertilization etc have been described but are not generally accepted

In the fresh blood the trypanosomes are colorless structures rapidly moving through the field with both translatory and rotatory motion In specimens fixed in one point and examined under high power the wavelike movement of the undulating membrane may be seen along one edge Details may be seen only after staining and the usual techniques and stains for blood are satisfactory Intense staining may be necessary to demonstrate the cytoplasmic granulations For fine cytological work films are fixed while wet in Schaudinn s fluid stained with iron hematoxylin and mounted in Canada balsam clarite etc

After using Giemsa s or Wright s fluids the cytoplasm and undulating membrane appear colorless to light blue and the nucleus kinetoplast flagellum and cytoplasmic granules red violet the shade being

about that taken by the leucocyte nuclei In the cerebrospinal fluid degenerated forms occur, and in thick drop preparations there may be some deformation but usually not sufficient to impede recognition

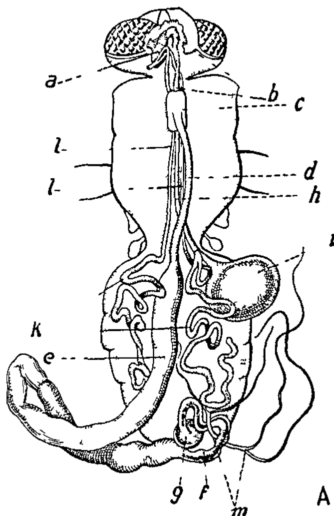


Fig 82 African Trypanosomiasis Cycle in Glossina Internal anatomy of *Glossina* a—pharynx b—oesophagus c—proventriculus d—fore intestine e f—mid and hind intestine g—rectum h i—duct of and the sucking stomach k—salivary glands l—ducts of salivary glands m—Malpighian tubules (Minchin and Stuhlmann from Neumann and Mayer)

Development of Trypanosomes

Trypanosomes are taken up from the peripheral blood by glossina and undergo a complicated cycle of development within the fly at the end of which they may be inoculated by bite on the occasion of another feed Glossina is infectious for the first 48 hours this is mechanical transmission and probably unimportant and again at the completion of the cycle whose duration is from ten to thirty five days or more During

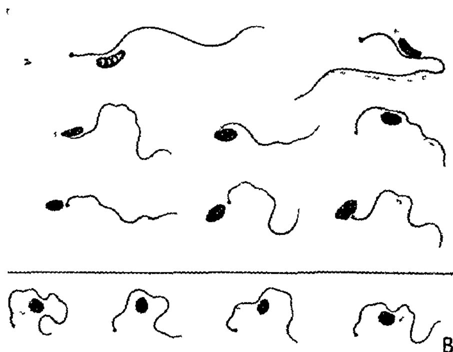


Fig 8b African Trypanosomiases Cycle in Glossina Developmental stages of *T rhodesiense* in *Glossina morsitana* Top row—proventricular types Middle row—forms from the salivary gland Bottom row—metacyclic infective trypanosomes ejected by a fly in attempting to feed × 000 (Bruce)

this period the trypanosomes undergo structural modifications (Fig 8b) and lose their ability to infect The final infective form is the metacyclic trypanosome which develops in the salivary glands This evolution is a multiplicative process as in malaria and not simply maturative as in

filariasis. It takes place entirely within the digestive tract and salivary glands and details will be given on a later page (see Transmission).

Cultivation of Trypanosomes

Cultural methods have not, on the whole, been satisfactory, and in contradiction to what is frequently stated, the NN or NNN medium is not generally suitable. Brutsaert and Henrard[101], using a modification of von Razgha's liquid medium[10], have been able to establish diagnosis where other methods failed. While the method has been useful, it is cumbersome and in case of execution cannot be compared to the usual bacterial culture. Brutsaert and Henrard carried on certain strains through numerous subcultures over more than one year. Reichenow[103] using the same medium had irregular results in isolation, and cultures once established died for inexplicable reasons. M. Lwoff and Ceccaldi[104] have shown that the variability in these results depends, at least in part upon the source of human blood used in the medium.

Weinman[10] recently described a solid blood agar which enables heavy growth to be obtained regularly from small inocula. No difficulty is experienced in maintaining the strains through numerous subcultures. The method is comparable in simplicity to a bacterial culture, has been equally successful with all strains tested, and both *T. gambiense* and *T. rhodesiense* grow readily upon the medium. It appears to obviate some of the difficulties of other methods and to promise well, but it has yet to be tested on patients. The foregoing applies to strains recently isolated; the same strains passaged several years in animals become uncultivable (unpublished).

Cultures have not yet been used as a routine method of diagnosis for reasons already cited. The cultural forms are predominantly those seen in the intestinal tract of *Glossina*, particularly proventricular forms, and cultures have not been infectious for animals.

Metabolism of Trypanosomes

Trypanosomes from the blood utilize large amounts of glucose[106] and oxygen[107]. von Brand and Johnson's finding that the insect and blood forms differ in several particulars is of interest[107]. *T. gambiense* cultivated on Weinman's blood agar giving principally insect forms consumed only -0 per cent of the oxygen of the blood forms of *T. rhodesiense*

Furthermore, cyanide, an enzyme system poison, which inhibits respiration catalyzed by heavy metals stimulated the blood forms and inhibited the culture forms leading to the suggestion that different enzyme systems may operate in the respective stages parasitizing the invertebrate and vertebrate hosts[107]

Various metabolic processes of the trypanosomes have been held responsible for the pathogenic effects on the host glucose consumption resulting lactic acid production and toxin elaboration von Brand concludes that not enough sugar is consumed to cause privation to the host lactic acid is not produced by the trypanosomes in metabolizing glucose and toxins have not been satisfactorily demonstrated[108] Glucose levels incompatible with life are observed in *T equiperdum* infections in rats this is due it is implied to the glucose consumption of the trypanosomes[109] The concentrations of parasites reached over 1 5 million trypanosomes per cu mm make close analogy with human conditions doubtful For various other theories asphyxiation increased serum potassium, etc , see [108, 109]

Species of Trypanosomes Concerned

Numerous species of trypanosomes have been described in African Sleeping Sickness all except *T rhodesiense* are now considered to be identical with *T gambiense*

The distinguishing features of *T rhodesiense* are based upon the following (1) Morphology a variable number of blood trypanosomes will have the nucleus placed in the posterior portion of the body, near to the kinetoplast and sometimes behind it These forms may occur in man[110] although most often they are seen after passage to small laboratory animals (2) Virulence *T rhodesiense* is virulent particularly in small laboratory animals *T gambiense* gives a more chronic type of infection (3) Serum sensitivity after one or more passages in animals *T rhodesiense* becomes sensitive to the action of human serum both in vitro and in vivo[111, 112] and may be destroyed by dilutions of 1 25 000 or more[113] *T gambiense* is unharmed [111] (4) Therapeutic response concentrations of arsenic compounds which are effective against *T gambiense* leave *T rhodesiense* relatively untouched (5) Epidemiology *T rhodesiense* is transmitted in nature by *G morsitans* and *G swynnertoni* *T gambiense* by *G palpalis* and *G tachinoides* (6) Geographical distribution *T rhodesiense* is found in East and East Central Africa

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number of derivatives develop at the time of each clearing of the blood and subsequent relapse and as many as twenty two immunologically different relapse strains have been so obtained These relapse sub strains come to resemble each other more closely after passage through *Glossina* (Broom and Brown[1 1])

It is a curious fact that *T gambiense* and *T rhodesiense* react in a very different way to normal human sera After several animal passages *T rhodesiense* becomes extremely sensitive to normal human sera whereas *T gambiense* does not[150 111 11 112] Although strains sensitive to human serum are infective for man[1] it is not known that humans actually become inoculated with such strains under natural circumstances for as Adams has shown after a single passage in *Glossina* the human serum sensitivity is greatly diminished[1-3]

Treatment

General Considerations

African trypanosomiasis comprises two therapeutic problems The early stage may be cured with relative ease and a number of compounds are available which will remove trypanosomes from the blood and lymph nodes Once the organisms are established in the brain the majority of these are useless and tryparsamide is the only drug which has won universal acceptance for its activity in cerebral cases Anything which *limits the use of tryparsamide such as toxic reactions or insensitivity of* the trypanosomes to it considerably worsens the prognosis Reports of increasing numbers of tryparsamide resistant cases are a matter for concern[6]

The course of treatment in most general use today combines the advantages of the available products and utilizes successively a very active trypanocidal agent such as antrypol or less often orsanine followed by tryparsamide In almost all cases the outcome will be favorable if treatment is instituted early enough In any given patient it becomes more doubtful as time progresses and poor when the case is advanced particularly when it involves *T rhodesiense* or resistant strains of *T gambiense*

There is a striking lack of agreement concerning the optimum therapeutic regimen This refers particularly to tryparsamide schedules in which total doses varying from 10 to 40 grams or more are being

T. gambiense is more widely distributed and particularly prevalent in the western part of the continent.

Since some of these criteria are known not to be absolute, e.g., the original morphological one, and as there is some doubt whether any of them are, the validity of *T. rhodesiense* has been subject to question. The term is useful and will probably persist so long as it is useful, although taxonomists may conclude that the rank to be accorded it is below that of a species. The difficulty, as so often is met with in dealing with microorganisms, is that extremes are easily recognized; it is the numerous intermediates which are difficult to classify (see, for example, Lester[8]). However unsatisfactory the present situation, the alternative view to admit but one species carried to a logical conclusion would entail that all the species be called *T. brucei*, now the name of an animal species not infectious for man[114].

Immunology

During trypanosomiasis no sterilizing immunity develops, except perhaps for the very few cases of spontaneous cures, which are cited in the literature and may have had an immunological basis. Antibodies against the trypanosomes are produced but to what extent they modify the course of the infection is not clear. In cured patients there appears to be residual resistance to reinfection since when returned to endemic areas they fail to become infected in the same ratio as the other inhabitants[11 7].

There is no immunological diagnostic reaction in wide use at present. The adhesion test sometimes employed is based upon the tendency of small particles to adhere to trypanosomes in vitro in the presence of specific serum. The test at first employed blood platelets as the indicator (Rieckenberg phenomenon); later it was found that bacteria or red blood cells could serve also (Brown and Broom[11]). Cold hemagglutinins also develop; these are of the auto- and iso- types, are active at low temperatures and the agglutination is reversible by warming to 37°C[116]. A complement fixation test has given Rodhain and associates satisfactory results in trials[118].

Immunological phenomena have been investigated more extensively in animals and for those interested the excellent critical review by W. H. Taliaferro[119] should be consulted, some more recent data being summarized by Culbertson[120]. Within each species of trypanosome there are immunologically different strains and reactions usually are strongest toward the homologous strain. In addition, from each natural strain

Tryparsamide is soluble in distilled water and usually is so dissolved to make a 20 per cent solution prepared extemporaneously and administered intravenously or more rarely intramuscularly[1,6] The usual single dose for an adult is 2 0 gms This is repeated every five to seven days, the total dose usually ranging between 20 and 45 gms varying with the strain response and previous treatment Single doses as high as 4 0 gms and series as high as 80 gms have been given Children s dosages have ranged between 0 03 gm[91] to 0 08 gm /kg[14] or more Chesterman[1,8] gave six to eight weekly injections of 0 07 gm /kg in the early stage and the same number of 0 09 gm doses in the cerebral phase

Tryparsamide penetrates into the central nervous system and is the only one of the drugs currently used in sleeping sickness which has this property in marked degree Hawking[17] found that after a single 3 0 gm intravenous dose (per 70 kg) the total arsenic in the spinal fluid was at 17 hours 0 41 gamma per ml at 4 hours 0 12 gamma and at 65 and 96 hours slight traces only Although it is less trypanocidal than other arsenicals (i e orsanine) its action in advanced cases makes it invaluable and the introduction of tryparsamide has improved the prognosis of advanced *T gambiense* cases enormously

It is of less utility in *T rhodesiense* cases as Pearce and Brown[1,8] predicted Keevill[16] found it of no use Fairbairn[14] finds that it has value but chiefly when the protein is below 0 04 per cent This fact and the growing limitation to its effectiveness in *T gambiense* infections due to the development of ever more numerous tryparsamide resistant strains[20] makes the finding of a substitute a matter of ever increasing importance

Tryparsamide Resistance — Often termed arsenic resistance this is as pointed out by Yorke[1,9] incorrect the resistance is to the non metallic portion of the compound and arsenic resistant strains which tolerate tryparsamide remain normally sensitive to sodium arsenite This resistance may be quite specific and Eagle and Magnuson[130] have described a strain of *T equiperdum* which spontaneously became 5 to 00 times more resistant to a derivative containing amino and amide groups whereas it retained normal sensitivity to methyl chloro or acid substituted derivatives Much of practical importance is involved and arsenic resistant strains which do not respond to tryparsamide have been found to be susceptible to other new arsenical preparations

Tryparsamide resistant strains occur naturally arise spontaneously in the laboratory and may be produced experimentally by administering

employed with an intermediate one of about 30 grams finding wide, if not clearly justified favor This variance arises from the different results which are obtained in different regions, and to a certain extent also from theoretical considerations The possible advantage of small doses is for some far outweighed by the risk of establishing resistant strains following subcurative dosage a procedure known to produce resistant strains in animals

In general the higher doses of tryparsamide are used in foci where treatment has been pursued for a long time, e g , the Belgian Congo, where 40 to 42 grams (per 60 kg of weight) of tryparsamide per treatment are given[1 4 31], conversely in Sierra Leone a total dose of 10 grams has given a cure rate of 85 to 93 per cent with 1 0 per cent or less dying during treatment[5]

Specimen Schedule

The procedure is based on the recent reports of Harding and McLetchie[1 1] The spinal fluid is examined before treatment for cells, protein or both again at its conclusion and one or preferably two years later Antrypol is administered first in three spaced 1 0 gm doses Between the first and second doses three weeks or more should elapse this interval having been found to reduce the number of toxic accidents resulting from subsequent tryparsamide therapy[5] The third dose of antrypol is given five days after the second, and tryparsamide is administered five days later, in 2 0-gm doses repeated at five day intervals Five injections of tryparsamide are used in Sierra Leone[7], five or preferably ten in Nigeria[1 11] and twenty in other regions

Products Active in All Stages

Tryparsamide (U S P) — Synonyms — Tryparsone, glyphenarsine tryponarsyl trypotan novatoxyl Tryparsamide is the sodium salt of 4-phenylglycylamide-arsonic acid or *N*-phenylglycineamide p arsonic acid[1 11] It is a quinquevalent arsenical, similar in structure to atoxyl the first anti sleeping sickness drug widely used It was developed by Jacobs and Heidelberger in 1919[1] and applied to experimental trypanosomiasis by Pearce and Brown Pearce in 1930 reviewed the clinical results obtained during the first decade[1]

The visual disturbances may come on with the first few injections At the outset they are purely subjective consequently patients should be questioned and examined before each injection According to Ridley[4] the phenomena progress in four stages (1) the first subjective symptoms mists, flickerings shimmering movements or objects and metamorphopsia, (2) within a few days there is a general lowering of vision with loss of the peripheral fields to even large objects this is followed by a marked loss of central acuity In all probability there is first a peripheral field loss to colors and small objects but due to incomprehension this may be difficult to demonstrate At this time the optic disks still appear normal (3) in about two weeks the disks appear pale there is no swelling nor vascular abnormalities At this time the patient may be completely blind with inactive three fourths dilated pupils (4) a period of recovery proceeding throughout three to six months. There may be complete return of central acuity with some improvement in the peripheral fields The pallor remains unchanged or progresses the retinal vessels are somewhat narrowed and near the optic disk the larger vessels show a white perivascular cuffing Recovery of central acuity is compatible with even extreme pallor of the disks but *then the peripheral limitation of the fields will be gross* Ridley *reported* on 33 cases 11 had temporary amblyopia 21 optic atrophy 16 with *recovery of central vision* 5 had permanent *amblyopia*

The visual disturbances most often occur during the first ten or twelve *injections*[4, 13] *They are reported to be more frequent in cases* with marked brain involvement the frequency increasing with the *degree of abnormality of the spinal fluid*[6] *so as to be twelve times more* common when the cell count is over 100 than when it is normal[13, 14] although at least *one author* Ridley[4] *found no such correspondence*

The pathological changes described in a case (Leinfelder[12]) consisted *principally of retinal lesions* with acute degeneration *of the* ganglion cells particularly peripherally and some degeneration of cells *of the inner nuclear layer there were no acute lesions of either the optic* nerves or optic tracts In the causation of these reactions probably both *toxic and infectious components are involved for while tryparsamide* produces the same effects in syphilis of the central nervous system yet in trypanosomiasis the *incidence increases* with the degree of involvement of the central nervous system

There appears to be *no certain way to avoid* the visual troubles Antrypol which does not cause blindness is believed to predispose toward visual disturbances *on subsequent* tryparsamide therapy[16, 14]

sub-curative doses. It is not known whether such strains usually arise by mutation or by selection, or whether to a certain extent both factors do not come into play. Whatever the mechanism, once a strain becomes tryparsamide-resistant this is usually, although not invariably[0], a stable character which persists through repeated fly cycles[131, 13]. It is accordingly easy to understand why tryparsamide resistance may be characteristic of a certain area, and that tryparsamide resistance is found with mounting frequency in the areas where treatment campaigns have been carried on the longest. Although arsenic-resistant strains may be less transmissible by *Glossina*[30, 33], the actual number of such strains encountered under natural conditions appears to be much greater than formerly. In addition to true tryparsamide resistance, cases may be erroneously so-called when the organisms are normally sensitive and the defect is actually one of absorption or distribution. True resistance is correlated with failure of the trypanosomes to bind tryparsamide[130].

Some idea of the importance of the question may be obtained from the figures of van Hoof[30]. In the vicinity of Leopoldville there were about 7 per cent. of resistant cases before 1938, whereas today more than half are resistant. In small foci this may take place with great rapidity, as Leraerts[76] has pointed out.

Toxicity of Tryparsamide. — Jarisch-Herxheimer type reactions are rare but may be of extreme severity with hyperpyrexia (107° F.), nuchal rigidity, Kernig's sign and death within 24 hours (Mackie[8]). Gastrointestinal intolerance has been noted; it is uncommon and usually temporary. Dermatitides have been observed. It seems that the detoxifying agent dimercaprol (B.A.L.) might be used in treatment to great advantage. Toxic effects upon the bone marrow resulting in granulocytopenia and/or anemia should, when they occur, be similarly treated combined with other suitable therapy, penicillin, transfusions, etc. Other reactions noted in syphilitic non-African patients include nitritoid or allergic responses, cerebral manifestations (psychotic, convulsive, aphasic) and peripheral nerve disturbances[133].

The most common serious complication of tryparsamide therapy is optic neuritis. Pearce[24], reviewing the literature in 1930, estimates that about 5 per cent. of the patients treated showed some visual disturbance and 1.8 per cent. had permanent impairment of vision. Ridley's more recent figures are similar, from less than 1.0 to 1.5 per cent. of optic atrophy[4], as are those of Kopp and Solomon[133] with a non-African clientele, 4.5 per cent. visual disturbances and 1.2 per cent. optic atrophy.

The most efficient dosage and administration remain to be determined before the product can be compared with tryparsamide Weinman and Franz[136] gave 0 1 mgm /kg intravenously daily for seven days and van Hoof[30] 25 mgm intravenously daily or every other day for 25 injections Payne and associates[140] report that a daily dose of as much as 75 mgm intravenously for three to five days was well tolerated

The majority of authors find melarsen oxide not at all or only slightly toxic in therapeutic doses (Weinman and Franz[136, 1] van Hoof[30]) however Culbertson Rose and associates[141] report severe toxic reactions encephalitis with recovery in two patients with doses which have elsewhere proved completely innocuous

Products Not Active in Advanced Cerebral Cases

These substances may be satisfactory when only minor modifications of the spinal fluid occur beyond some ill defined borderline perhaps 30 cells and 30 milligrams of protein they are ineffectual

Antrypol — synonyms Bayer 205 germanin naphuride suramin belganyl suramin sodium (U S P) The original formula was kept a proprietary secret but Fourneau synthesized what is accepted as the identical substance fourneau 309 or moranyl Naganol is a form for veterinary use[2, 40, 1]

Moranyl (antrypol) is the symmetrical urea of *m* aminobenzoyl *m* amino *p* methylbenzoyl 1 napthylamino-4 6 8 trisulphonate of sodium It is soluable in distilled water and usually is dissolved 1 0 gm in 10 c c of water and administered intravenously Single doses as high as 1 5 or 0 gm may be given safely (Manson Bahr[61]) The single dose for children is 0 03 to 0 035 gm /kg infants and nurslings are given 0 2 to 0 3 gm intramuscularly (Ceraerts[6]) Total doses of 10 grams are used[14, 61] however when antrypol is to be followed by tryparsamide a smaller number of injections are made often three Although an injection schedule of once weekly is widely recommended if antrypol is to be followed by tryparsamide a pronounced reduction in toxic effects will be obtained by allowing three weeks to elapse between the first and second injections (Harding[5])

Antrypol acts energetically on both *T gambiense* and *T rhodesiense* in the blood and lymph nodes therefore used alone it may effect a cure before cerebral trypanosomiasis is established Its effect is very long lasting and for that reason it has been used in chemoprophylaxis It does

However this may be, in combined treatment toxicity may be greatly reduced by a rest period of three weeks between the first and second antrypol injections (Harding) When symptoms appear, treatment should be suspended at once, whence the utility of careful questioning and examination before each injection Dimercaprol (B A L), active in other forms of arsenical poisoning, may very well prove to be of use in optic neuritis although no reports on it in this condition are yet available Sodium thiosulphate has been recommended, Ridley[4] and Chesterman[136] found it of no utility Large doses of yeast did not influence recovery[4]

The resumption of treatment is a very delicate matter Sometimes tryparsamide is better tolerated after a rest interval[6] but it is always dangerous to proceed[4] Choice in this distasteful dilemma has been between possible blindness and nearly certain death

At present there is no satisfactory solution to the problem One of the new tervalent arsenical compounds (melarsen oxide) is stated to be active in the cerebral form (Weinman and Franz[136, 137], van Hoof[30]), and it may prove of particular value in cases intolerant to tryparsamide, but at present it is being used on a trial basis only

Melarsen Oxide — Recently introduced and still being assayed details about this compound are nonetheless given since it is in that extremely rare category of drugs which are active in meningoencephalitic cases and effective against tryparsamide resistant strains

Melarsen oxide is a tervalent arsenical 2-(4-arsenosoanilino) 4 6 diamino s triazine dihydrate also referred to as *p* (2,4 diamino s triazinyl 6)-aminophenyl arsine oxide It is derived from melarsen a quinquevalent compound synthesized by E A H Friedheim and has been prepared by Friedheim[138] and by Banks and collaborators[139] A succinct review of the experimental pharmacology, chemistry and physics based upon the work of Banks Gruhzit and associates has been made by the author[137]

Melarsen oxide was introduced into therapy by Weinman and Franz[136] who found it of unusual promise They reported it[136, 137] to be active in cerebral cases producing clinical improvement and a reduction in cell count in even advanced cases This very unusual quality was in addition to its action upon the trypanosomes occurring in the blood and lymph nodes and it was effective both orally and intravenously van Hoof[30] has confirmed the activity in cerebral cases and in addition found the compound active against trypanosomes resistant to tryparsamide

better to abandon treatment cases of anuria followed by uremia and death are known

Therapeutic Failures with Antrypol — Naturally resistant strains occur[39] but are uncommon Because of their rarity and because this property when induced is diminished on glossina passage antrypol resistance has posed no important problem as yet Relapses after therapeutic doses should not necessarily be interpreted as resistance there may be defective accumulation of antrypol in the blood Hawking[113 117] found wide variations in the plasma concentrations from one individual to another abnormally low concentrations explained relapses in three patients in two of which resistance of the trypanosomes to the drug was evaluated and found normal He accordingly recommends that treatment be controlled by chemical estimation when necessary and feasible[113]

Quinquevalent Arsenicals — *Orsanine* also known as Fourneau 270 is analogous in structure to atoxyl being the sodium salt of 2 hydroxy 4 acetylaminophenylarsenic acid It is given in 8 10 per cent solution made extemporaneously in distilled water which may be warmed to hasten solution The dose varies from 0 35 mgm /kg the ceiling is 0 gm for an adult 0 5 1 5 gm are used for children It is given in a series of twelve injections one a week either subcutaneously[19] or intramuscularly or intravenously[21]

It is said to be more trypanocidal than tryparsamide but is not effective in meningoencephalitic cases beyond the initial stages Sice[21] states that it will cure 98 per cent of early cases of Gambian sleeping sickness Ledentu (in Joyeux[1]) reports 7 to 39 per cent relapses Despite its rapid and energetic action since it may cause optic neuritis by itself and since it will often have to be followed by tryparsamide, most persons prefer to treat the initial stage with antrypol

Atoxyl is also known as soamin (according to Castellani and Chalmers[19] soamin is monoacetylated atoxyl) trypoxyl arsanax arsamin sodium aminarsonate sodium arsanilate and arsanilic acid It is 4 aminophenylarsonic acid and is generally employed as the sodium salt[12] Introduced into the therapy of sleeping sickness by W Thomas it was the first compound effective in the disease to be widely used Today it is scarcely ever employed but subsequent improvements tryparsamide and orsanine based on atoxyl and showing close structural analogies to it are in use

Tervalent Arsenical Compounds — That tervalent arsenicals were potent agents has been known for some time Salvarsan for example gave apparent cures in about 60 per cent of cases before a rise in the

not penetrate into the cerebrospinal fluid in detectable amounts even when present in the plasma in high concentrations (Hawking[143]). It will not cure cerebral cases of any gravity. There is some disagreement about its use in borderline cases. Kellersberger[14] states that it has no effect on the cell content of the cerebrospinal fluid; in his group, with 20 to 500 cells, reductions in the cell count were observed rarely and then only temporarily. Keevill[144], however, had 6 cases with abnormal cerebrospinal fluid cell counts treated with antrypol alone (5 with 5 gm., 1 with 3 gm.); two to three years later all were in excellent health, five spinal fluids being obtained all with normal cell counts. Fairbairn[4] reports that cures may be obtained with slightly abnormal fluids, even when trypanosomes are present, the limit apparently being 30 mgm./100 c.c. of protein in the spinal fluid. These apparent discrepancies may be reconciled by the suggestive observation of Peruzzi[9] that although trypanosomes penetrate into the central nervous system early, they cannot maintain themselves at first; this may be the period when by clearing the blood antrypol appears to have an action in the earliest state of cerebral involvement.

Toxicity of Antrypol.—In about 1 case per 1,000 the injection may be followed by collapse and death has followed a single 1.0-gm. dose (Fain[14]). This idiosyncratic reaction may be avoided in part by the initial injection of a trial dose of 0.2-0.3 gm.[146, 7] Freshly opened ampoules should be used; such reactions have followed the use of antrypol opened three days previously.

Patients should rest in a cool place after the injection, for not uncommonly there are immediate shock phenomena, usually mild and transitory, consisting of nausea and reddening of the face or, when more marked, of vomiting and loss of consciousness[14]. Other types of reaction include fever within two-three hours and usually of brief duration; various cutaneous eruptions variable as to date of appearance and type; hyperesthesia usually localized to the extremities but sometimes generalized, followed about a week later by desquamation in the same regions; signs of renal involvement[14]. This last is the most frequent complication.

About 50 per cent. of the patients in Fain's series[145] had urinary albumin following a dose of 0.025 gm./kg. If it appeared in the first few days the prognosis was good; if on the seventh day or later then it was often more serious, persistent and accompanied by granular cylinders and red blood cells. Mild forms which clear up spontaneously are not a counter-indication to resumption of treatment; often there is less reaction to subsequent doses. If serious intolerance is encountered it may be

better to abandon treatment cases of anuria followed by uremia and death are known

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Trivalent Arsenical Compounds — That trivalent arsenicals were potent agents has been known for some time Salvarsan for example gave apparent cures in about 60 per cent of cases before a rise in the

spinal fluid cell count was marked[140] The great defect of these compounds lay in the inability to modify the course of cerebral infection One which has been recently introduced is p-(P-arsenosophenyl) butyric acid also known as 70A Experimental trials indicate that it is rapidly effective in clearing the blood and lymph nodes of trypanosomes even strains which are tryparsamide-resistant but is ineffectual in meningoencephalitic cases[1 0 136 13 0] Studies on combined use with tryparsamide are now in progress

Antimonial Compounds — Tartar emetic is employed occasionally for tryparsamide-resistant cases It is however, of no value in the treatment of the meningoencephalitis[21 10] Given as a 1 to 2 per cent solution with 50 to 100 mgm at each injection eight or ten weekly injections are made to total 0.4 to 1 0 gm[21 11] It may be given at the same time as antrypol and then followed by tryparsamide[6] Fouadin has been used successfully to remove trypanosomes from the lymph nodes[136] and in one case accomplished this after 74 gm of tryparsamide had failed to do so[1 1]

The Amidines — These are guanidine compounds developed from synthalin as a starting point by Yorke and his collaborators (Yorke[1]) Three have been widely used stilbamidine propamidine and particularly pentamidine Pentamidine is 4 4 Diamidino diphenoxypentane

In general their effect is similar to that of antrypol pronounced action in the early stage with persistent effects which has led to their use in chemical prophylaxis In cerebral cases none are effective (Lawson[13] Lourie[134] van Hoof and associates[1 1] Harding[1] Saunders and associates[1 6])

The place which these amidines will fill in the therapy of sleeping sickness is not clear at the moment As will be shown van Hoof and associates consider pentamidine superior to antrypol for chemoprophylaxis

For completeness it should be stated that the antibiotics in most current use have shown no promise for trypanosomiasis, for a report on penicillin see Nelson[1 7] on streptomycin Merchant[1 8]

Antitoxic Products

Dimercaprol known also as B A L (British anti lewisite) is 2 3 dimercaptopropanol It has proved of distinct value in the treatment of arsenical intoxications agranulocytosis dermatitis and even hemorrhagic encephalitis Although reports of its use in optic neuritis have

not yet been encountered it would seem logical to employ it in these cases Prepared in oil in 10 per cent strength it is administered intramuscularly and preferably early in adequate amounts and frequently The following schedule is recommended first 48 hours 3 mgm/kg every 4 hours third day 4 injections each of the same dose, then 2 injections daily for 10 days or until recovery[1 2]

There are some toxic but transitory symptoms, headache burning sensation of the gums nose eyes and skin profuse lacrymation salivation and a feeling of constriction of the thorax These may be cured by 0 6 c c of 1 1 000 epinephrine given intramuscularly and prevented by 25 mgm of ephedrine sulfate given one half hour before the injection[1] Dimercaprol may be expected to diminish the parasitic action of tryparsamide before effecting detoxification, if analogy with mapharsen is valid (Ercoli and Wilson[161]) This is a point to be determined compounds of mapharsen with substances similar to dimercaprol have, contrary to prediction considerable trypanocidal activity[162]

Para Amino Benzoic Acid was found by Sandground and Hamilton[163] to reduce greatly the toxicity of tryparsamide without affecting its trypanocidal qualities Unlike dimercaprol it is useless once the toxicity is declared being active only when injected prior to at the time of or very shortly after the tryparsamide[164]

Criteria of Cure

A patient may be considered cured when after a course of therapy blood and lymph node examinations are repeatedly negative and the spinal fluid cell count and protein values are reduced to normal It may not always be possible to bring the last two to completely normal values but no result over 10 white cells and at the most 25 milligrams of protein per 100 c c is acceptable (Sicé[16] Fairbairn[19]) The final lumbar puncture preferably should be made not earlier than 15 months after the end of treatment for in the interval there may be temporary fluctuations in either direction (Harding[7])

TRANSMISSION

African trypanosomiasis is contracted from the bite of an infected *Glossina*, more rarely it is transmitted directly from mother to offspring

exceptionally infection results from some other mechanism The first is by far the most important

Insect Transmission

Glossina — Flies of this genus are dark in color, 7 0 to 14 0 mm in length have two well developed wings and a pair of prominent eyes The proboscis ensheathed in the palpi is conspicuous, it terminates basally in an enlarged bulb and the apparatus is held horizontally except when feeding Tsetse flies can be distinguished from the majority of other dark colored flies (house fly stable fly) when at rest by the crossed position of the wings scissors-like over the abdomen (Fig 9)

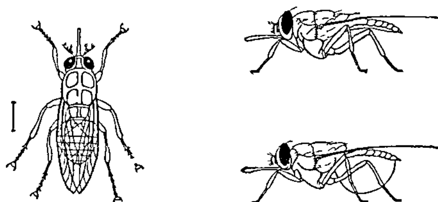


Fig 9 Diagram of *Glossina palpalis* view from above and from the side before and after feeding (Todd)

The terminal portion of the antenna (arista) is distinctive, the under side being naked the upper surface appearing quite hairy due to secondary branching of the bristles Of great value in generic classification is a peculiar character of the wing venation common to all and said to be unique (Hegh[1])

Once *Glossina* were far more widely distributed than now as proof of past presence in the United States four fossil species of *Glossina*, pertaining to the tertiary period of the Miocene were found buried in volcanic ash in Colorado At present *Glossina* is known only from tropical Africa There is a questionable report that *G tachinoides* occurs in the southern tip of the Arabian peninsula in the vicinity of Aden

Within this African area, estimated at 4 500 000 square miles (Swynnerton[3]), the distribution is discontinuous (see Fig. [illegible]) the flies being particularly present along the great water courses (Congo, Volta, other rivers and their tributaries).

Life Cycle of Glossina.—The period from adult to adult requires from 43 to 73 days with extremes of 39 to 95. Newly hatched females are ready for copulation within a few hours. A larva develops within the mother which takes "milk" from a papilla in the uterus, undergoes two intra-uterine moults and is expelled some 15 to [illegible]0 days after copulation for the first birth, about 10 days for subsequent ones.

Glossina is then larviparous but in nature the larva is seen rarely. It is active, burrows into the soil to a depth of 1.0 to [illegible].0 cm. and within an hour and a half at the outside undergoes a final third moult becoming the pupa. The final larval skin or puparium rapidly changes its characters and within 4 to 5 hours is hard and dark brown. The pupae of *Glossina* are motionless and barrel-shaped with two prominent lobes at the posterior end. They are distinctive in appearance and the species usually can be determined from pupal characters.

The duration of the pupal stage varies somewhat with the species and environmental conditions. *G. palpalis* requires 3[illegible] to 33 days at about [illegible]6 C. *G. morsitans* [illegible]1 to [illegible]5 at [illegible]9 C.; the limits range from 17 to [illegible] days, and males require a day more than females. Then the adult forces its way out of the puparium through the end opposite the lobes and [illegible] to 5 hours later has the appearance of a normal adult. No food may be taken the first day but it feeds avidly by the second (Hegh[4]). Males require a blood meal before copulation, females at least one, and according to Vanderplank[14] [illegible] before the first larva and then at least one for each succeeding larva (Bequaert[15]).

Biology of Glossina.—Both sexes are hematophagous and transmit trypanosomes. They feed voraciously and often. At a single meal a female may absorb 1.6 times its body weight in blood or 0.485 gm. and a male 1.3 times, 0.3 gm., and they will refeed about every 30 hours. Blood is the exclusive diet but within that limit the flies are catholic and will feed on mammals, birds and cold-blooded vertebrates, notably reptiles. Food preferences of the different species are marked and of great practical importance, i.e. otherwise excellent potential vectors may feed preferentially on animals.

They are strong fliers, and the possible flight range, for example when in pursuit, is very great; for *G. morsitans* a ten mile flight has been recorded, five miles is not too exceptional and one to two not uncom-

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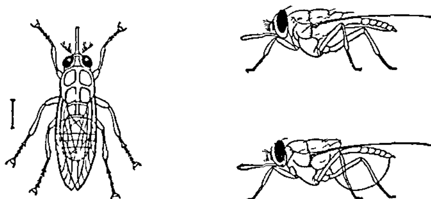


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mon' *G palpalis*, although a strong flier appears to dislike open spaces and clearings of 200 yards are said to be sufficient to deter it The flight usually is accompanied by a characteristic buzzing noise but it may be silent in the early morning when the temperature is low[168]

The flies are chiefly active during the morning and afternoon, avoiding the heat of noon and coldness at night They are attracted by motion and attempts to flee may simply draw them on They respond definitely to colors Khaki is reported to be the worst, i e the most attractive color tested then come red blue black white and yellow They are very responsive to changes in humidity, accordingly local distributions fluctuate during the wet and dry seasons

Important Species of Glossina — Of the twenty two species of *Glossina* in Africa there are five principal vectors for the human disease *G palpalis* and *G tachinoides* for *T gambiense*, *G morsitans*, *G swynnertoni* and *G pallidipes* for *T rhodesiense* Others often cited are *G fusca* and *G brevipalpis* The habitat and food preferences of these five species show wide divergences as will be seen in the discussion of epidemiology and control

Trypanosomal Cycle in Glossina — Development within the fly involves a series of migrations Taken in with the blood, the trypanosomes first pass caudad and multiply in the posterior portion of the mid intestine These trypanosomes which are non infectious, then migrate a second time cephalad as far as the proboscis undergoing meanwhile structural modifications and assuming first the proventricular and then the crithidial form (Fig 8) From the proboscis they pass into the salivary apparatus and move caudad once again to reach the salivary glands wherein the final infective metacyclic trypanosomes are produced During feeding or in the probing preparatory to it, trypanosomes in various stages are ejected by the fly the infection being set up by the metacyclic forms of which from one to over 11 000 may be ejected at a single feed (Robertson[94 96] Taylor[169], Brumpt[3], Fairbairn and Burtt[3]) No significant differences in the cycles of *T gambiense* and *T rhodesiense* are reported save by van Hoof and associates[1 0] who cite certain peculiarities in appearance and grouping of the salivary gland forms of *T rhodesiense*

The cycle in *Glossina* is then multiplicative as in malaria, not simply maturative as in filariasis Once established a salivary gland infection persists for long periods in most cases for the life of the fly but there is no hereditary transmission

The cycle requires 12 to 40 days with extremes of 10 to 50 Fortunately the trypanosomes complete their evolution in only a small proportion of infected flies, in wild specimens 1 0 per cent is considered a high salivary gland infection rate under laboratory conditions 10 per cent an average figure Under special conditions Taylor[169] and van Hoof and associates[171] have obtained 75 per cent of salivary gland infections

A number of variables influence the salivary gland infection rate a minimum temperature is required a higher temperature is favorable[1 16] the host is important as is the duration of the infection in the host[1 1] certain strains of trypanosomes give higher rates than others finally the fly will give higher rates if pupated at elevated temperatures[1 2] The number and complexity of these factors make it particularly difficult to estimate how closely certain laboratory experiments approximate natural conditions One additional point deserves particular mention the reported reduced transmissibility of arsenic resistant strains[20] this has not sufficed to prevent an enormous increase of resistant cases in certain regions

Thus far we have discussed only cyclical transmission it has been suggested that *Glossina* may also act as a mechanical conveyor While this is possible (Bruce and associates[174]) it remains to be shown that this mechanism is of importance

Other Insects —Mechanical transmission by other insects also has been suggested Laboratory transmission of either *T gambiense* or *T brucei* has been achieved by species of *Stomoxys Culex*, *Aedes Tabanus* and *Mansonia* What relevance this has to natural transmission is problematical While it is not an impossibility that an individual case may be so transmitted now and again Strong Bequaert and Cleveland could find no convincing proof of a single such case It cannot be emphasized too strongly that African trypanosomiasis is established only where *Glossina* is found that it has been introduced time and time again where other bloodsucking insects abound and has never obtained a foothold unless *Glossina* were present The situation is different for certain trypanosomiases of animals which originally African and glossina transmitted are now established elsewhere The most notable case is *T vivax* found in Central and South America the West Indies and Mauritius (Adams[175] Johnson[176]) The organism is maintained without *Glossina* this adaptability possibly being related to the simple type of development the whole cycle taking place in the proboscis According to Adams[1] the only other example of a usually tsetse borne trypanosomiasis outside continental Africa is *T congolense* which has been

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Trypanosomiasis is a disease of sparsely settled areas or of small communities and conversely densification of the population beyond a certain point entails activities which are unfavorable to the fly All ages sexes and races are susceptible Activities which bring individuals or groups into contact with *Glossina* increase the disease incidence in that group This will vary with the species of fly concerned Where *G palpalis*, a riverine species is the vector boatmen will be particularly

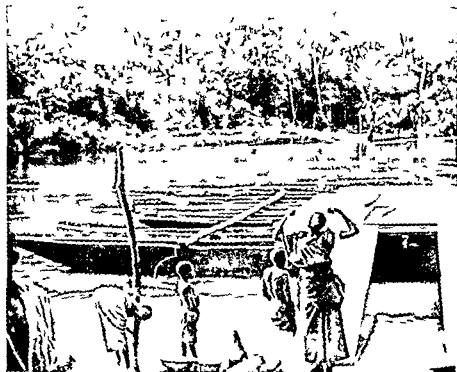


Fig 10 *Glossina palpalis* characteristic feeding grounds Ferry crossing Belo Belgian Congo

infected if the women wash at the river taking their children with them then the incidence in these two groups may be as high or higher than in the males (Fig 10) *G morsitans* not limited to rivers feeds particularly on wild game so that hunters may be most affected and the disease be uncommon in females A great deal has been made of the superior attractiveness of a black skin to a white one in my experience and with

found in Zanzibar Island Neither *T gambiense* nor *T rhodesiense* multiply in various species of *Triatoma* or *Ornithodoros*, which are natural and experimental vectors of Chagas disease (Packchanian[1])

Congenital Transmission — In two cases David and Pape[18] demonstrated trypanosomes in the peripheral bloods of both mother and child at the time of birth and also in blood from the umbilical cord thus proving the possibility of transplacental transmission Another record of an infant probably infected congenitally is of a child born in France who was hydrocephalic at birth and febrile shortly thereafter the mother subsequently being found to be infected (Darré and associates[43])

Such cases generally are considered to be extremely rare but in the present author's opinion a correct assessment is yet to be made The causes of infant mortality are not well determined in Africa Greggio[4] years ago produced evidence that the incidence of spontaneous abortions and of deaths in early infancy was much higher in the offspring of infected women than in the rest of the same population Precisely what caused these deaths or abortions is not known since there were no autopsies but it seems not unlikely that at least in some cases the trypanosomiasis exerted its effect by direct congenital infection of the infants

Other Means of Transmission — Coitus is often said to be a method whereby infection is contracted this is apparently based on circumstantial evidence reported by Koch (Strong[11]) whether the supposed mechanism involves true sexual transmission for example spermatozoidal or some other is not stated

Contact with infected blood can of course produce infection so that transfusion errors and accidents during surgery or in the laboratory may account for a few exceptional cases

Epidemiology

The necessary factors for the perpetuation of the disease are the fly the trypanosome and man Favoring factors are those which increase opportunity for infection either by close man fly contact or by producing suitable conditions for maintenance or spread of glossina Animals enter into the epidemiology as a food source for the glossinas but their importance as reservoirs of trypanosomes probably has been overestimated

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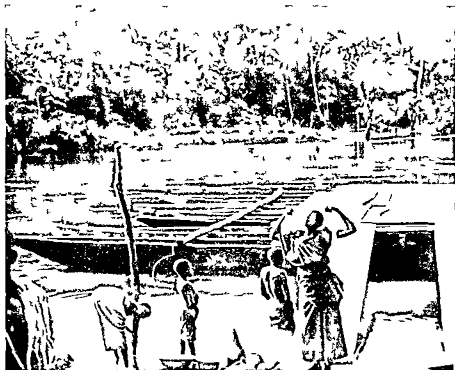


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G. palpalis at least this is quite relative and no cause for complacency, the flies attack a light skinned person with great avidity

Of the very greatest importance is the relationship between *Trypanosoma brucei* found in cattle and game and the human trypanosomes It has been and is held that *T brucei* is the same as *T rhodesiense* because of the identical appearance and cycle in the fly and similar behavior However the two must be distinguished for *T brucei* does not infect man There are areas where *T brucei* is common, numbers of cattle and game are infected the vector *G morsitans* attacking man readily and constituting a nuisance yet cases of sleeping sickness are unknown, *e g* Zululand (Curson[1 9]) Furthermore it has never been possible to establish infection in man with trypanosomes from wild animals either by the inoculation of blood or the feeding of infective flies (Corson[180]) More than 00 attempts have now been made and all have failed[3 180] Brumpt[181] calculated that with 135 inoculations from 3 to 27 infections should have resulted if the two were identical trypanosomes These negative results of course do not preclude an eventual success but even so *T brucei* would not then have been shown to be a sleeping sickness hazard of any immediate importance Exceptions to be considered are two laboratory infections with supposed *T brucei* (cases Lanfranchi and Vaucel), the identification or the purity of the strain has not been established van Hoof[0] once observed *T brucei* to persist in the blood for as long as three weeks

An entirely different question is the role of animals as reservoirs of *T gambiense* and *T rhodesiense* Experimentally it has been shown that they may so serve for *T rhodesiense* has persisted in animals as long as ten and a half years during which time it retained infectivity for man (Corson[18] Fairbairn and Burtt[7]) Formerly it was believed that antelopes particularly were very important but Duke who has studied the matter over a period of years concluded that antelope, though undoubtedly able to serve as a reservoir are not perhaps so dangerous in this respect as has hitherto been supposed Game alone apart from its bad effect on food and crops is not harmful save in as much as it may attract tsetse[40] Fairbairn[30] still considers the wild animal reservoir adequate to maintain endemic *T rhodesiense* infection in depopulated areas but the evidence is circumstantial and inconclusive There is also a possible danger from domestic animals in particular the pig[183 30] A summary of this extensive and inconclusive field is difficult but it may be said that thus far animals have not been shown to play an important part in the epidemiology of the disease as reservoirs of the human trypanosomes

It is as a food source for *Glossina* that animals do have undeniable importance. An instance often cited is the great rinderpest epidemics which took place in Southern Africa between 1890–1900. Killed off great numbers of the game, following which in certain areas tsetses disappeared and with them tsetse borne disease. The sequence of events is clear but not the causation; great numbers of animals were left alive and rinderpest blood in itself has no ill effects on *Glossina*.[8] However, that may be, a control measure used in Tanganyika apparently with success against game tsetse involves the considerable reduction of wild land animals.

Control, Prophylaxis

The control of trypanosomiasis is an extremely complex problem. The disease is very widespread and carried by a number of vectors with different habitats and requirements. Accordingly procedures of value in one region may be worthless or even harmful in another. Additional complications arise when, as often happens, it is considered necessary or expedient to attempt to control both cattle and human trypanosomiasis at the same time. Finally, the most direct and simple methods may have to be discarded because of unfavorable agronomic consequences.

According to Swynnerton[22] there is a 2,000 mile wide band across tropical Africa which is infested with one or more species of *Glossina* and is a hotbed of human or animal trypanosomiasis or both. He estimates this area at 4,500,000 square miles, finds the flies advancing in Tanganyika, Nyasaland and Northern and Southern Rhodesia and states that "in respect of diversity and extent combined no other entomological problem approaches it." The discussion here can be but summary; for fuller documentation from the fly aspect see Swynnerton[5]; a recent review by Wilcocks, Corson and Shepard[4] also evaluates treatment control.

Antitrypanosomal Measures

Chemoprophylaxis.—Antrypol, which persists in the blood for 5 to 9 months after a single intravenous injection (Hawking[143]), has been the most used for this purpose. In the field very nearly complete protection for 3 months is given by a single injection of 1.0 gm, or somewhat preferably 2.0 gm.[155, 18, 34, 6] It has been particularly valuable for the quick reduction of a tryparsamide resistant focus (Lemerts[6]). When applied

in endemic regions the method should be preceded by examination and appropriate treatment of those already infected and followed by an examination of those protected to make certain that a cryptic infection which has reached the central nervous system, has not taken place These cryptic cases often if not almost always develop in infected persons who were not diagnosed prior to drug administration

The amidines have been used lately for the same purpose by van Hoof and associates, who employ preferably pentamidine isethionate in intramuscular injection using 3 0 mgm per kilogram The results reported thus far have been excellent, there is little toxicity by this route and the period of protection is about 6 months or double that with antrypol[181 3] Examination prior and subsequent to treatment is required also with this method

Treatment Campaigns —Mass treatment, when continuously applied has resulted in a notable lowering of the incidence of cases A reduction to a figure as low as 0 2-0 3 per cent of new infections per annum has been attained in the Belgian Congo but it has been impossible to reduce it below this minimum[30] Total eradication has been accomplished occasionally in a limited area by this means alone *viz* the Lake Albert region with 150 000 inhabitants and 5 per cent new infections annually in 19 3 The disease was eradicated by systematic treatment of all patients although contact between man and glossina persisted and for 8 years the disease has not re established itself[30] A disquieting concomitant of the method is that following tryparsamide therapy resistant strains are reported with increasing frequency in those areas where mass campaigns have been utilized on the largest scale

Whether an epidemic can be controlled by mass treatment alone is not agreed upon (see Wilcocks and associates[8]) The method seems to be less valued by those who deal with *T rhodesiense* outbreaks and to have best results in new and spreading *T gambiense* foci and poorest results in old strongholds of the disease, this is perhaps related to the development of tryparsamide resistant strains mentioned above

Antiglossina Measures

These will vary with the habitat breeding places feeding preferences etc of the different species Humidity requirements vary considerably and have served for a rough classification Bequaert[1c], for example discusses three groups of which two are of interest to us here

Riverine species of Glossina, e.g., G. palpalis. Adults require dense shade and high humidity. They find optimum conditions along wooded shores of lakes and forested banks of main rivers and affluents if a stretch of open water is nearby. Bequaert does not find them along smaller forest streams completely enclosed and shaded over by trees. Where streams are adjoined by continuous forest the flies do not penetrate therein much over 150–200 yards. They feed in the absence of man on animals frequenting wooded river banks, crocodiles, monitors, hippopotami, wild pigs, etc. These features contrast strongly with those of the next group.

Savanna Species.—G. morsitans and G. pallidipes. These thrive even where the environment is very dry part of the year. They prefer grassland usually with scattered trees, bushes or thickets which provide a certain amount of light shade. Often they are associated with large herds of game which they attack even in brightest sunlight. *G. tachinoides* is a riverine species but requires less moisture and is more hardy than *G. palpalis*, whereas *G. swynnertoni* is found associated with *G. morsitans*[3].

Direct Antitsetse Measures

Traps, poisons and repellants are used. The trapping of the adult tsetse is very effective for certain species, of little value against others. They may be taken by hand or by mechanical device and numerous types exist. Hand carried screens consisting of black cloth covered with a sticky material (Maldonado procedure) were used very effectively in ridding the island of Principe of *G. palpalis*, a daily catch of 500 per cloth was common and 1,500–2,000 not rare. By this means over 110,000 flies were caught in ten months at the start of the campaign[4]; such screens are still in use. A stationary motionless variety, the Harris trap, has proved very effective against *G. pallidipes*, each trap accounting for about 1,000 flies per month in good weather; by multiplying the traps enormous numbers may be disposed of: 2,000,000 with 983 traps in September 1941[4]. This type however has little to no effect on *G. morsitans* or *G. swynnertoni*, which are more attracted by traps containing some part which is in continuous motion, rotating or escalator traps. For further details see Swynnerton[32].

Pupae may be hunted and trapped also, at times with less effort than the adults. Spots suitable for larvipositing apparently require a combination of features, humidity, shade, consistency of soil, etc., which may

result in one or a few sites for pupae of adults which are spread over a much greater area Such sites serve as traps, when left undisturbed, visited periodically and the pupae harvested

Poisoning of flies may be effected by insecticides, and when the species concerned is attracted by domestic animals the latter may be treated and serve as baits Pyrethrum is effective[18], and one application will prevent feeding for 24 hours Fatal poisoning is not instantaneous, and during the few seconds required the fly while probing, may eject infectious trypanosomes This danger would appear to be somewhat minimized by the direct trypanocidal effect of the pyrethrum[166]

Diphenyl dichloro trichlorethane (DDT) is toxic for all the species investigated although variably so more for *G morsitans* than *palpalis*, for example A single application to oxen had a marked effect for one week less for the second and none for the third Vanderplanck[168], who reported these results thinks that in attacking tsetse who favor cattle (*G morsitans swynnertoni pallidipes*), it should be feasible to flood an area with a number of treated animals equal to the estimated wild animals and that this should result in a marked reduction in the flies and be far more economical than spraying DDT is not trypanocidal, and since it requires some seconds to act the possibility of infection during probing exists

Repellents seem only moderately effective Findlay and associates reported some activity[188] for indalone and for 622, which is dimethyl phthalate 6 parts indalone 2 parts 2-ethyl hexanediol-1-3 2 parts[189] Neither prevented flies from settling and biting but persons treated with 622 had only about 20 per cent as many bites as the controls Efficiency diminishes four hours after application

Indirect Antitsetse Measures

Reduction of Food Supply — This method used chiefly against game tsetse involves killing or driving out the wild game and for permanent results usually is combined with measures to prevent re entry of game in the area Results will depend on how severely the food supply is depleted a shooting campaign worked well in Southern Rhodesia but was not satisfactory in Tanganyika where *G morsitans* feeds on wild pig which could not be killed off efficiently[8]

It should be clearly realized that by such a method the flies may be forced into closer contact with man For this reason it has been consid

ered wiser in certain areas not to attempt to reduce the game (e g Nigeria [7])

Alteration of the Environment — Quite aside from any conscious effort to control glossina it appears that the normal activities of man tend to create conditions adverse to it In so far as defined these act through reduction of game and in certain areas through clearing and cultivation of lands on a larger scale than formerly both of which tend to follow densification of the population Bequaert[10] mentions several regions where the fly has disappeared as the area developed without specific antifly measures As to a definition of sufficient population density communities of 3 500 to 4 000 were considered the smallest which could look to freedom from glossina within two years of establishment (Hemming and associates[106]) Epidemics are discouraged by populations of less than 10 persons per square mile or more than 100 Fairbairn reports for Tanganyika whereas 16 to 80 persons creates favorable circumstances[3]

Measures consciously applied have included the most diverse and apparently contradictory procedures In some regions burning of the brush has been followed by a reduction in the local tsetse population e g *G morsitans* in Uganda elsewhere prohibition of fires with the resultant densification of the growth has proved beneficial e g *G swynnertoni* certain regions of West Africa Against even a single species a method may work well in one area poorly in another Many variables are concerned and for the intelligent application of this type of control it is necessary to know not only the habits of the species concerned and its feeding requirements etc but also as much as possible about its habitat Thus fire exclusion is good against *G morsitans* in certain parts of East Africa supposedly by increasing the grass matting which in turn produces a humidity so elevated as to be unfavorable to the pupae it is bad in Nigeria against *G morsitans* since it would provide shelter against otherwise unfavorable conditions

Clearing of vegetation in one form or another is used very widely At times communities are moved into burned over areas which then are kept clear or since total clearing is expensive to make and maintain and may cause soil erosion partial discriminative selective and other types have been described Clearings along water are particularly effective against *G palpalis* and instead of total clearings the Symes block method has been used with success Blocks of riverine bush one or two miles in length are separated by 1000 yard clearings Paths are then cleared along the river bank and these are patrolled by flyboys daily

or several times a week. Rapid reductions to very low catches result. Since the method is economical and has proved successful in such different areas as Lake Victoria, the Kenya rivers and the Sudan[11, 192, 8], it seems destined to come into wider use.

The measures already described, clearings, burnings, densification of growth, game reduction, etc., may be applied also to prevent the re-entry of glossina or to its extension into adjacent territory.

Breaking of the Contact between Man and Infected Tsetse

This has been effected by removal of villages to glossina-free areas, the latter to be abandoned or rendered habitable according to circumstances. In general abandonment alone is favorable to glossina since it permits of the growth of brush and increase of animals[190].

It is of equal or greater importance to avoid introducing the infection into a glossina-infected but sleeping sickness-free area. Restriction of movement of infected persons has been used widely, and in some regions "sanitary passports" indicating freedom from infection are required of natives before they can travel.

Application of Available Measures

The goal always should be carefully defined: it is one thing to protect a village against sleeping sickness, it may be quite another to render the same area completely glossina-free so that cattle raising will be successful. Measures applicable to an established community will be necessarily different from those used to sanitate an uninhabited area preparatory to settlement.

A preliminary step should be a careful entomological survey to identify the actual vector in the area; it is not enough to know what species of glossina are present. For example *G. morsitans* is an excellent potential vector, yet it has been found in the sleeping sickness regions of the Belgian Congo (Katanga) (Rodhain and associates[193]) and in the Sudan (Hunt and Bloss[192]) without playing any important part in maintaining the local infection; the same may be true for *G. palpalis*, which was present during an epidemic in Uganda where the principal vector probably was *G. pallidipes* (Mackichan[9]).

Undoubtedly the best results will be obtained from a combined therapy antifly campaign Treatment of the infected combined or not with general chemoprophylaxis usually will cause a marked drop in the *incidence of new cases and in an emergency this may be put into effect* while the entomological survey is being made Then with the latter completed fly control measures can be decided upon whether to move or to remain if the latter whether to clear or encourage growth and how to do each whether to drive out game or to leave it alone whether to build barriers isolating the community from outside flies and game or no etc Final decision will be found to depend at least as much on non medical factors such as ultimate effect on agricultural productivity or soil erosion on removal or changing of food supplies and occupations of the population as upon the purely health problems

A venture of the greatest interest is the Anchau settlement in Northern Nigeria There it is proposed to keep a 600 square mile area now inhabited by 50 000 persons fly free Besides the purely medical problems the project has involved a host of other considerations some of which it would seem of sufficient importance to determine failure or success These include resettlement and building of new villages study and introduction of suitable and often new crops improvement of live stock rebuilding of villages maintenance of clearings and other antitsetse measures introduction of schools education attraction of population etc It is anticipated that the general health level will improve and that as the economic value of the area increases it will become to an increasing extent self supporting[1, 2]

For individual prophylaxis the visitor to endemic areas may protect himself for months by a single injection of antrypol or probably of pentamidine Exposure to infection may be reduced by so dressing as to diminish the exposed areas, trouser cuffs should be placed inside boot tops or thick leggings etc the reported attractive power of khaki suggests avoidance When in heavily infected fly territory repellents may be of value applied to the face and other regions which cannot be *satisfactorily clothed Glossina will enter houses so that screening may* be of value since the fly is not nocturnal the use of mosquito bars is more advantageous for protection against diseases other than sleeping sickness except perhaps during the afternoon siesta

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PART II

CHAGAS DISEASE

Synonyms — American trypanosomiasis trypanosomiasis (schizotrypanosomiasis) cruzi locally doença do barbeiro, opilaçao *(pro parte)* and canguary *(pro parte)*

Definition and Characteristics

Chagas disease caused by *Trypanosoma (Schizotrypanum) cruzi*, is a progressive non contagious insect transmitted disease endemic in the Americas. Outstanding clinical features are fever edemas enlargement of the lymph nodes cutaneous manifestations of varied types cardiac abnormalities and particularly in infants a meningoencephalitis which usually is fatal It is a long lived infection evolving characteristically in acute and chronic phases The presence of immature multiplicative forms of *T cruzi* in the tissues is distinctive Transmission is effected by winged bloodsucking insects *Triatoma*, *Rhodnius* and related genera

History and Prevalence

Knowledge of the disease was obtained by an unusual reversal of the customary progress Prior to report of the first human case the etiological agent and cultivation of it were described as were the vector methods of diagnosis experimental host animals and major features of the epidemiology Carlos Chagas established all this in his early publications from 1909 onwards and then proceeded over a period of years to give a description of the disease which quite appropriately subsequently has been known by his name[1] [2] Lacerda however in 1904 may have been the first to record the American trypanosome in man[4] By 1909 he had found it in the spinal cords of three patients with beri beri and inferring a causative relation employed the name *Trypanosoma beriberiano*[5]

Medical interest was for many years sluggish the matter seemed more of a curiosity to be encountered in certain regions of Brazil than a problem but between 1935 and 1940 the situation changed somewhat abruptly

Chief credit for the current medical evaluation of Chagas' disease goes to Mazza and his collaborators, who in a long series of careful field studies in Argentina showed that the prevalence was far greater than previously supposed This stimulated investigations in other countries the finding was confirmed and it now seems that Chagas' disease should be recognized as an important cause of invalidity and death throughout large regions of South America

Vianna[6] launched the study of the pathological substrate of the condition, describing the intracellular multiplicative forms in convincing detail although they had been reported previously by Hartmann[6A] The evolution of *T cruzi* in *Triatoma*, described by Brumpt and da Silva in 1912 is now generally accepted, infective forms are found in the feces, and as Brumpt subsequently maintained it is the feces which are infective not the bite, infection is "contaminative" not "inoculative" As will be seen, this explains one of the peculiar clinical features of the disease

The disease was and is difficult to diagnose, the complement fixation reaction introduced by Guerreiro and Machado in 1913 is, with modification in wide use today Brumpt from 1914 onward has used the xenodiagnostic method which consists in feeding uninfected insects on the suspect and subsequently examining them for trypanosomes[8] Since the bugs are hardy and require only spaced feeding they may be sent by mail to and from a central laboratory from the field and the method has proved most convenient for rural investigations

That the importance of the disease was undervalued for so long may be readily understood in the twenty-eight years from 1909 to 1937 only 117 cases were reported Then Mazza and his group showed what systematic surveys in rural areas would unearth, and in Argentina, not thought to be particularly involved 630 cases were discovered by this one team alone from 1935 to 1940, and by 1944 1,300 cases were on record[9] It seems probable that in many of the endemic areas it would suffice to look for the disease to find it and since the majority of such regions still have not been surveyed adequately we consequently do not have even a fair estimate of the number of infected persons Talice[9] considers that in certain areas as high as 10 to 30 per cent of the population will be found to be infected In Uruguay alone there are an estimated 700 000 persons living in *Triatoma*-infected huts and continually exposed to infection this it is calculated should yield some 4 000 to 5,000 new cases annually[10]

Another recent finding of the very greatest interest is the probable occurrence of *T cruzi* outside of the Americas It now appears that *T cruzi* is endemic in parts of Asia producing in animals and experimentally in the insect vector infections which in all important features are thus far, indistinguishable from those caused by American strains Brumpt as early as 1909[11] foresaw that Chagas' disease might have an Asiatic distribution and Malamos[12] investigating spontaneous infections in monkeys from Java (*M cynomolgus*) gave convincing proof that in all particulars investigated including morphology in the blood and tissues development in the insect host and infectivity for laboratory animals the organism was indistinguishable from *T cruzi* As yet in Asia as in the United States no spontaneous human cases have been described

In the United States the history is recent Kofoid and McCulloch in 1916[13] found a trypanosome in a California specimen of *Triatoma protracta* Later Kofoid and Donat[14] proved the trypanosome of *T protracta* to be *T cruzi* and at the same time reported a naturally infected wild host the wood rat (*Neotoma*) Since that time a number of infected species of North American triatomas and of wild animals have been found due to the investigations of F Donat Wood S F Wood D J Davis A Packchanian and others[15] Although at least one strain has been shown experimentally to be infective for man no spontaneous human cases have been reported thus far This does not appear to be due to failure to recognize the disease in the Texas area at least for of over 3 000 human sera including more than 500 from *Triatoma* infected shelters only one fixed complement and it could not be proved that this person was infected (Davis and Sullivan[16])

As may be judged the history of Chagas disease still is in the making It can no longer be considered a minor hazard of a restricted area of Brazil it is now known to be a serious problem in South America although of still undetermined incidence and to be far more widespread than the previously accepted designation American trypanosomiasis would indicate

Geographical Distribution

In the Americas *Trypanosoma cruzi* is found from 41 south latitude in the Argentine[1] to about 33 north of the Equator in the United States but Wood and Wood[17] give 38 as the northern limit in the United

States considering a trypanosome found in bats to be *T cruzi*, a by no means certain matter Human infections are less widely distributed but have been reported from every South American country except the Dutch and English Guianas, in Central America from Salvador, Guatemala Costa Rica and Panama[18] and in North America from Mexico

Within the United States infected rodents and/or vectors have been found in California Arizona New Mexico and Texas[19 20] Although these vectors feed on man, no spontaneous human cases have yet been reported Presumptive vectors exist throughout the southeastern and southern Atlantic states but it does not yet seem to be known whether infected insects or animals occur in this area

In Asia the distribution is completely unknown The evidence for its occurrence is that infections with *T cruzi* have been found in Asiatic monkeys examined in Europe and in the United States Malamos' identification of the parasite found in *M cynomolgus* monkeys from Java is complete and convincing[12] Previously Brumpt had reported *T vickersae* from the same species[21 11], Terry *T rhesii* from *Macacus rhesus* and Et Sergent a trypanosome from *M sinicus* (in 23) Brumpt[3] considers these trypanosomes to be all *T cruzi* and states that the geographical range of the hosts includes India Burma Siam the Malay Peninsula Indo China and southern China In this vast area no human case has yet been brought to light A possible Asiatic vector is *Triatoma rubrofasciata*

Clinical Description

Chagas disease is a very long lived infection giving two classes of symptoms first those of an acute infection with certain individual characteristics and second as the infection is prolonged increasing manifestations of localization usually in the heart with corresponding symptoms of weakening or failure As will be discussed in detail the severity of Chagas disease varies according to locale so that estimates of it have been found at both extremes of the gamut

Incubation Period

Fourteen to 16 days elapsed before first symptoms in three cases where the date of infection was determined accurately (E Chagas , Herr

and E Brumpt[5] Pacheco[15]) On indirect evidence an interval as short as 4 to 5 days is reported, the upper limit is not known but in cases with mild symptoms it may appear very prolonged

Onset and Invasion

The initial symptoms usually consist of either ocular or cutaneous manifestations

Ocular symptoms result from an edema which usually is unilateral and involves both lids The edema progresses rapidly although remaining localized and within a few days of appearance has so intensified that it may be impossible to open the eye on the affected side (Fig 11) The skin about the involved eye is tense red violet in color but usually pain



Fig 11 Acute Chagas disease early edema about the eye (Mazza and associates)

less There is a slight conjunctival discharge but any marked inflammation suggests some additional cause as medication or secondary infection By the time swelling is pronounced the local lymph node usually the preauricular more rarely one of the submaxillary or parotid groups or both has become enlarged The enlargement is quite distinct the nodes are freely movable and only slightly painful on palpation An important additional sign is the frequent enlargement of the lower portion of the lacrymal gland (the accessory lacrymal gland of South American authors

and B N A terminology) This dacryoadenitis becomes readily evident when the lids are drawn up and out by traction above the lateral commissure (Fig 12) Fever and other general symptoms to be described accompany these local manifestations

The early ocular symptoms, either complete or in various combinations have been termed the 'oculo-nodal complex' or sign of Chagas Romaña The frequency with which they occur varies according to the region from 70 per cent in Argentina to 25 per cent in Venezuela[9] and this may perhaps be correlated with the varying virulence of strains The duration is from 1 to 3 months occasionally 5 [3], and certain features



FIG 12 Acute Chagas disease dacryoadenitis left eye (Talice)

may recur later in the disease In pronounced cases involvement of both eyes exophthalmia or edema involving the whole face may be seen, and conjunctival granulations may form in any type of case

The *ocular manifestations formerly were considered* to indicate invariably the point at which the trypanosomes entered the body but Mazza [9] brings evidence that they may follow upon blood dissemination This view has been stressed in regard to the dacryoadenitis, which whatever the pathogenesis is considered by Talice[30] to be one of the most constant signs occurring in some 40 per cent of patients

The cutaneous early lesion, sometimes termed a "chagoma", is less frequent than the ocular being observed in about 20 per cent of the patients Often found on the uncovered regions of the skin, it starts as a small red-violet macule frequently painful and hot to the touch, sur

rounded by a larger edematous area The lesion frequently containing a small centrally located darker portion enlarges and in about a week comes to measure 4 to 7 cm but does not become more than slightly raised The skin and surrounding tissue are indurated for a distance of 1 to 2 cm, and the lesion itself cannot be pinched readily into folds nor can it be moved on the underlying tissues with normal ease The regional lymph nodes sometimes are enlarged After lasting two weeks or so the lesion crusts over (Fig 13), desquamates and regresses slowly often leaving a slightly pigmented scar[9, 18, 9] Any suppuration suggests secondary infection



Fig 13 Acute Chagas disease initial skin lesion left arm two weeks after first appearance (Mazza and associates)

In a more unusual type of onset which does occur in perhaps 10 per cent of the cases the first symptoms are of a polyserositis with edema Finally in nurslings there are often no external manifestations whatsoever

Clinical Types

Acute Common Type — The usual case begins by one of the methods described, the symptoms being accompanied by fever The latter may be intermittent, continuous with morning remissions or irregular The acme usually not above 102°F does reach 104 F or more in children and in severe cases and in such patients tends to be either continuous or to have only slight remissions After lasting some two weeks there is a gradual decline throughout about a week to normal Thereafter sudden short lived bouts of fever take place, and such febriculae may recur throughout a long period

A distinctive if inconstant feature, of the fever is the double or even triple daily rise described by Mazza[31] If the temperature be taken every four hours or oftener then in some 30 per cent of fever charts several peaks will be found during a 24-hour period This observation has been confirmed[9], it is unfortunate that leishmaniasis, one of the other diseases giving this type of curve, coexists with Chagas' disease in many regions

The pulse is fast and remains so during afebrile periods a rate of 100 to 150 accompanying a normal or slightly raised temperature[3, 18, 27] Occasionally bradycardia is noted[6, 7] as well as various irregularities of the pulse but such phenomena being more common during the chronic cardiac phase are discussed later

Edemas are a common sign They do not retain the digital imprint and give an elastic sensation on palpation The edema may be either localized to the face lower portion of the abdomen or ankles or be generalized with predominance in the regions cited and accompanied by fluid in the pleura and peritoneum Facial edema usually can be distinguished from the oculonodal complex for either it does not involve the eyes or does so as a part of the general facial swelling and then is bilateral

A generalized enlargement of the lymph nodes appears during the first weeks and may persist for years The nodes remain mobile are not painful and it is considered typical that the groups involved contain individual nodes of varying sizes The spleen and liver can be enlarged also at times but this is not a constant finding

Cutaneous manifestations of the most varied types have been described by Chagas, Mazza and collaborators and others In addition to the early lesion already described the following are encountered

Exanthematic types — These include the morbilliform which has been mistaken for measles the urticariform which sometimes is pruriginous papular and scarlatiniform varieties and a polymorphous type

composed of heterogeneous macular elements These eruptions usually appear during the first two months and persist for a few days to two weeks or so [23,24,25]

Nodular Formations — These are the usual type of the chagomas of South American authors They are rounded firm subcutaneous elements 1 to 2 inches in diameter movable but not freely so and usually painless Deep seated elements are not visible and require palpation when superficial the covering skin is reddish violet but not adherent The nodules frequently are multiple as many as 50 being reported in one patient and they may coexist with one of the exanthemata In nurslings there is a peculiar localization in the fatty tissue of the cheeks Eventually the nodules regress often leaving a retracted scar[22,34]

Ulcerative lesions situated on the foot lip or elsewhere have been described by Mazza These are said to be small punched out and visibly different from the ulcers of cutaneous leishmaniasis

Necrosis of the skin in patches described by Chagas[3] does not have a clearly determined etiology and Talice[9] noted frequent secondary infections in such lesions

Acute Meningoencephalitic Type — This is seen most frequently in nurslings and the very young it evolves rapidly and often is fatal[3,38] Convulsive seizures are the common symptom They initiate the illness in the majority of cases and in the remainder are preceded by edema cutaneous lesions or less often ocular manifestations The convulsions are bilateral or rapidly become so and are more marked in the region of the head and superior extremities

During an attack the head is thrown back usually to one side with conjugate deviation of the eyes and frequently nystagmus The breathing becomes stertorous the face cyanotic and spume fills and then escapes from the mouth At the same time the forearms are flexed on the arms and the arms on the trunk in tonic contraction interrupted from time to time by clonic movements These seizures last from a few seconds to ten minutes there may be from one to thirty a day and in general they increase in intensity and duration as the disease progresses becoming at the end semi continuous

Other signs include fever which may be absent or slight at the outset but usually is high during the terminal period edema about the hands feet or in the face enlargement of the liver which may be considerable and less often enlargement of the spleen and lymph nodes

These cases often terminate by death within a few days to two weeks if not patients who recover frequently have permanent mental or

physical defects, intellectual deficiency, contractures, paralyses, etc (see chronic nervous manifestations)

Cardiac Type, Acute and Chronic — The cardiac form has been studied particularly in Brazil and Argentina, countries where the disease is severe The following discussion by necessity is based chiefly upon the available detailed reports However it will be emphasized that the disease is reported to be much milder in other regions and for such areas the data here presented must be so interpreted (see clinical varieties)

The heart is a favored site for parasites and for lesions Although cardiac and general symptoms may and do coexist during the acute phase signs of heart involvement of extreme gravity usually do not occur until later It is the frequency with which severe myocardial lesions develop after a cure has been suggested by regression of the acute symptoms which causes the prognosis in late Chagas disease to be so reserved

Mazza[1] followed 164 patients with Chagas disease and found that 138 or 84 per cent later presented cardiac abnormalities only 26 16 per cent did not In another study of a group which had passed through an acute attack 50 per cent gave electrocardiographic tracings indicating abnormal myocardial functioning and this figure was considered too low to be representative since young age groups predominated (Dias and associates[18])

In general the cardiac type occurs in individuals between late child hood and middle age from 10 to 45 years old It is rare below 5 years of age and the majority of patients do not outlive 50 or 55 according to data from Brazil[18, 34] whereas elsewhere the outlook is considered much more favorable Mosely and Miller[40] are quite correct in emphasizing that myocarditis during the acute stage may be seen in adults as well as in children

The myocardial lesions are detectable clinically by signs of cardiac insufficiency and irregularity in rhythm or radiologically by enlargement of the heart The electrocardiogram is said to be of particular value since it is often the only way of detecting the lesion it has been used for this in surveys of rural populations

The symptoms are variable and consist of palpitations, dyspnea epi gastric and precordial pain and more rarely vertigo and syncope These symptoms often start before one year and not infrequently one to two months after the acute period[17] When some degree of cardiac insufficiency is reached there is marked edema with enlargement of the liver which is slightly sensitive and gives a sensation of heaviness

The blood pressure usually is normal or lowered and readings above

120 for the maximum are rare Roentgen ray examination almost always shows some degree of enlargement The transverse diameter is more enlarged *than the longitudinal the right ventricle is larger than the left* The aortic image usually is not abnormal in uncomplicated Chagas' disease and if so found suggests some concomitant process

Arrhythmias of various types are outstanding and particularly com *mon are the disturbances following upon heart block* C *Chagas called* it the disease with a permanent slow pulse par excellence and the Stokes-Adams syndrome is said to be more frequent than in any other chronic myocarditis[9] From 183 patients with chronic Chagas disease 90 ab *normal electrocardiographic tracings were obtained Forty two had* some degree of auriculo ventricular block and 35 an intraventricular right branch block Twenty four had ventricular extra systoles In about 10 per cent of the patients a total auriculo ventricular block occurred The most frequent block was of the right intraventricular branch seen in 39 per cent of the above series and in 18 per cent of the whole group of chronic cases curiously the left branch usually was not involved (Dias and associates[14])

In a study limited to chronic cardiac cases E Chagas[9] reported that about 90 per cent of the group showed electrocardiographic changes indicating alteration of auricular or ventricular complexes and/or extra systoles Sudden death occurred in some 23 per cent of these patients and most frequently in the categories just mentioned This incidence is higher he believes than in any other disease

A symptom complex considered quite typical consists in slight edema of the skin arrhythmic pulse signs of enlargement of the heart and an arterial pressure with low maximum said to be not above 90 mm Hg and normal minimum (Torres[41])

The evolution of chronic cardiac cases is extremely variable The majority of patients after some years go on to a state of cardiac insufficiency after several bouts of decompensation each of which yields less well to rest and medication than the preceding Eventually there is little or no response to therapy and asystole results with death from right heart failure and congestive insufficiency Death is frequent in the first decades of life[1] and the majority of patients do not live beyond 50 to 55[18, 9]

The prognosis is at present poor the disease is progressive and therapy now available may be expected to delay this progress but not to arrest it permanently Of immediately poor prognosis are (1) manifestation of advanced cardiac insufficiency with much fluid in the cavities

(2) pronounced enlargement of the heart even without insufficiency and (3) certain types of arrhythmia as auricular flutter and crises of ventricular extra-systoles the latter indicating death within a few days[11]

As pointed out this very unfavorable view of the sequence of events high incidence of cardiopathy developing in infected persons with an important proportion of these eventually invalided and dying from the infection may and probably does not apply to all cases of Chagas' disease For example Talice in Venezuela has found that many patients pass through a mild early stage and then appear cured

Chronic Nervous Manifestations — These may be the sequelae of a childhood meningoencephalitis or according to Borges Fortes[4] result from an infection acquired as an adult It does not seem to be established whether and how often the lesions are progressive

Paralyses of cerebral origin are the most common manifestation[3, 18, 2] Particularly frequent are cerebral diplegias double hemiplegias and pseudobulbar syndromes[9] Little's syndrome congenital cerebral diplegia is such a frequent manifestation that visiting neurologists report seeing more cases of this sort in a few days in endemic areas than in the rest of their professional lives elsewhere[4]

Less frequent and associated or not with the foregoing are symptoms of cerebellar involvement epileptiform manifestations involuntary movements of various sorts intellectual deficiency[9] and anarthria and aphasia[9, 4]

Eventually contractures and vicious postures appear In juvenile patients there may be developmental defects failure of the genital organs to mature absence of secondary sexual characters or a general tendency to infantilism associated with marked mental debility[9]

The prognosis appears to be somewhat difficult to make In moderate cases the full extent of the damage may only become evident in later years whereas the severe cases improve somewhat but are usually left with some morphological reliquiae and some degree of intellectual impairment

Chronic Conditions Possibly Related to Chagas' Disease — The curious "mal de engasgo (Spanish mal de los atorados") also known as spasmodic dysphagia esophagismus megaesophagus etc which is particularly prevalent in the areas where Chagas' disease occurs has been conjecturally related to it The condition starts as a rather sudden difficulty in swallowing At the outset this is intermittent but it progresses so, that in a few years the patient may have to follow each mouthful with a glass of water and to eat in the standing position in order to force food

and water into the stomach Eventually practically all the ingesta are regurgitated Surgical intervention on the esophagus has been followed by complete relief[42] X rays show stenosis and/or dilatation at the cardial end, the difficulty subjectively may be localized at any height

This spasmodic dysphagia is said to be endemic in Brazil is thought to be of infective origin and patients usually have an enlargement of the spleen and lymph nodes Its possible relation to Chagas disease is based upon reported geographical concordance frequency with which *T cruzi* is isolated from dysphagic patients i e in 22 of 48 patients[43] and the commonness with which symptoms of the two conditions are found in the same patient The relationship if any is by no means clear no histological account of the excised esophagal tissue has been encountered It would be of interest to know whether *T cruzi* infection will reproduce the condition in animals outside the endemic areas and to compare the frequency of spasmodic dysphagia in endemic and non endemic regions

The view that a form of endemic goitre is caused by *T cruzi* is now generally abandoned its basis coexistence in the same patient being due to geographical coincidence *T cruzi* is found rarely in the thyroid either in man or infected animals

Clinical Varieties

The severity of Chagas disease is differently appreciated in different regions The preceding clinical description has as stated been based chiefly upon cases from Brazil and Argentina where symptoms are marked In Chile Gasic[44] finds the disease milder and patients often reach the chronic stage with no recall of any acute period Similarly in Panama Johnson and Rivas[45] state that in non fatal cases symptoms and physical signs usually are absent and if not are mild indefinite and consist of general malaise and indefinite fever

The prevailing view correlates the difference in severity with variations in virulence of the infecting strains and there is strong experimental evidence in support of the opinion Probably the ability to infect man fluctuates just as widely

In Mexico the infection was known to exist for some time before a single human case was brought to light and in the United States despite widespread infection in rodents and in insect vectors feeding on man the first naturally contracted human case is yet to be found

Diagnosis

T cruzi usually is demonstrated following examination of the blood or more rarely tissues by cultural methods or by the infection of animals or clean insects When these fail a presumptive diagnosis may be reached by immunological reactions



Fig 14a *Trypanosoma cruzi* appearance in thick drop preparations Deformation avoided (Brumpt)

Direct Examination

Trypanosomes are in general scanty in the blood, a single negative examination does not have much value and indicates the need for repetition to be made preferably during febrile periods They are more frequent with certain strains (Fig 14a) and in children, where from 400 to 1 200 may be seen in a single drop[17]

Although trypanosomes can be found in fresh blood preparations or in films it is usually a saving of time to make stain and examine a thick drop preparation at once even then they may be discovered only with great difficulty. The organism is extremely fragile and the usual thick drop technique almost invariably leads to laceration or destruction of



Fig 14b *Trypanosoma cruzi* appearance in thick-drop preparations Following usual techniques (Talice)

the flagellum and undulating membrane. This may make recognition difficult for the completely unaccustomed observer but once studied there is usually no subsequent difficulty. The trypanosomes shown in

Fig 14(b) are typical of the deformed type and are not likely to be confused with other micro organisms Deformation may be avoided by exposing the drop of blood to osmium tetroxide vapors, then drying and staining as usual Talice[9] recommends Errecart's method Fix the blood wet 1 drop of blood to 3 or 4 of fixative (formol 40% 1 c c, acetic acid 0 2 c c saline 100 c c) Let dry and dehemoglobinize with distilled water (or if necessary 0 5% acetic acid) and wash Stain 20 minutes with Giemsa solution (1½ drop per c c) discard and stain 70 minutes with fresh Giemsa solution It is said that preservation is good and all structures stain satisfactorily

Although biopsies are rarely used for diagnosis, lymph node sections have revealed parasites when blood examinations and xenodiagnosis failed[10] Skin lesions also often contain parasites Splenic puncture is not advised although it may occasionally permit diagnosis[4] the organism usually is not present in the spleen and the risk involved seems unjustified Finally the organism has been isolated from the cerebrospinal fluid in meningoencephalitic cases (C Chagas[18])

Indirect Methods of Examination

Cultures — T cruzi usually grows readily on cell free media although there may be some difficulty in isolation The N N or the N N N varieties (rabbit blood mixed with nutrient or plain agar) are the most widely used It is advisable to inoculate a number of tubes say 6 if the infection is very light the tubes should then be incubated at room temperature (± 25 C) and examined weekly for 8 weeks

Cultural methods should always be used when direct examination fails Additional positives may be so obtained but not all patients will produce a positive culture and success is less likely during the chronic phase There is room for improvement in the method and various suggested media are discussed later (see Etiology)

Animal Inoculation — Mice and guinea pigs are the most used and since infectivity for different animals varies with the strain it is preferable to utilize several of each The animals should be as young as is convenient and inoculated with blood intraperitoneally giving as much as tolerated

Young dogs are considered the most susceptible by several authors and rats cats monkeys rabbits and others also have served successfully

Xenodiagnosis — This procedure introduced by Brumpt[8] utilizes

uninfected insect vectors which are fed upon suspects and then examined Considered by many to be one of the most sensitive methods available it has given results of particular value in the investigation of chronic cases where trypanosomes are extremely difficult to demonstrate This suitability derives from the almost unfailing infection of insects which have been exposed, this in turn is favored by the large quantities of blood absorbed a nymph of *T megista* ingesting almost 0 9 gm of blood at a single feeding and one of *T infestans* 0 435 gm

It has the disadvantage of requiring a rearing station for the insects which however are very easy to maintain and to require a relatively long period before results are available An advantage in addition to sensitivity is that the insects, being very hardy may be mailed back and forth from a central laboratory to field units For regions difficult of access or poorly equipped medically this may be the most convenient and practical method In practice 5 to 10 specimens usually late stage nymphae or adults and preferably the vector for the region are used They are allowed to feed to repletion during 30 minutes Fed insects then are separated from the others some are examined at the end of a month either by dissection and examination of the intestinal contents or following forced expression of feces if negative the procedure is followed after another month with the remainder[38]

Serological Methods —The complement fixation reaction has been widely used since its introduction by Guerreiro and Machado particularly in the modifications of Kelser[41] and Davis[42] As yet a satisfactory evaluation of the method is not possible This is due in part to the multiplicity of techniques employed rendering a comparison of results difficult and in part to the insufficient identification of positives and the inadequacy of various types of negative controls

Fixation takes place in animals by the fifth day in man by the end of the first month and probably earlier False negatives are said to be rare during the acute phase False positives are obtained in a high percentage of cases of leishmaniasis and possibly also chancroid but only rarely in syphilis The conclusions warranted at present seem to be that in proved cases it rarely fails and in unproved cases if positive it is of some presumptive value if leishmaniasis and chancroid be excluded The significance of a negative result in supposed chronic patients is not clear Additional information and a discussion of other less well established immunological tests is given later in the section on Immunology

Prognosis

For reasons previously presented the prognosis is variously evaluated In general during the acute phase death is exceptional except for the usually fatal meningoencephalitic form In Uruguay where the disease is fairly mild the death rate in all acute cases is probably under 10 per cent [9]

It is in regard to the long-term prognosis that the most marked regional variations appear In Brazil where severe forms are frequent,

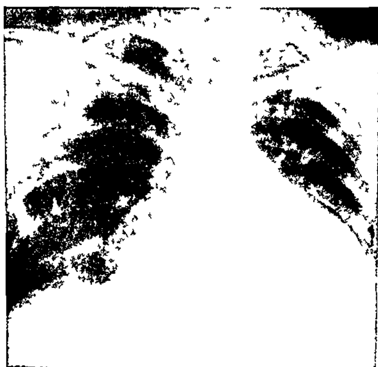


Fig 152 Chronic Chagas disease cardiac form x ray and autopsy photograph of the same case (Dias and associates)

there is an incapacity for strong physical labor which is progressive and due to growing cardiac weakness The latter is a frequent cause of death which may be due to either sudden myocardial failure or to gradual and ever-worsening periods of cardiac insufficiency As we have noted the patient who lives beyond 50 to 55 years, is considered exceptional[39] Where the disease is mild the tendency seems to be to consider many

of the patients recovered once they have passed through the acute period While this may be the case long term studies with detailed cardiac examinations through many years will be required before the view is justified



FIG 13b Chronic Chagas disease cardiac form heart block Stokes Adams syndrome death at age 23 (Dias and associates)

PATHOLOGY

Although the most important changes are in the heart and central nervous system *T cruzi* is capable of developing in extremely varied sites It has been observed in the myocardium central nervous system at all levels striped and smooth muscle thyroid ovaries cortical portion of the adrenals (Chagas[3]) bladder thymus liver spleen lymph nodes

blood vessels, skin lacrymal gland and conjunctiva (Mazza and associates [36, 40, 41] Crowell [42] Dao [47]) Corresponding to this is the lack of restriction in the type of cell invaded, reticulo endothelial cells muscle cells vascular endothelial cells, neurones microglial and neuroglial cells fat cells of the skin, etc

Gross Findings

At the post mortem examination some degree of subcutaneous edema is frequent accompanied or not by excess fluid in the peritoneum, pleura and pericardium The lymph node enlargement observed during life is found to be general and to include the mediastinal and mesenteric chains The heart is often enlarged (Fig 15b) Although the left side may be more involved usually the enlargement is due to dilatation rather than to hypertrophy and predominates on the right side Petechial hemorrhages may be found particularly beneath the epicardium and in the subendocardial layers Moderate enlargement of the liver and spleen is customary the liver often having a fatty appearance The lungs and kidneys appear congested but not otherwise remarkable In meningoencephalitic cases the meninges are congested and edematous however, exudate if present is slight in amount The cut surface of the brain may show scattered punctate hemorrhages but descriptions of large areas of softening have not been encountered

Microscopic Findings

Heart — Cardiac lesions are probably the most frequent of all and usually the most noteworthy Also when parasites are scanty, the heart may be the only site where *T cruzi* can be found

The pathological findings are of three chief types, (1) an inflammation predominantly interstitial at the outset, (2) destruction of muscle fibres and (3) the etiological agent *T cruzi*

The inflammation is both diffuse and focal and may reach an intensity greater than in any other acute myocarditis (Torres [41]) The infiltrating cells usually present in very large numbers occupy the space between adjacent muscle fibres this space appearing much enlarged and the fibres accordingly widely set apart from one another (Fig 16(a)) Where necrosis has taken place wandering cells may be present within the fibres themselves The cells are predominantly monomorphonuclear, micro

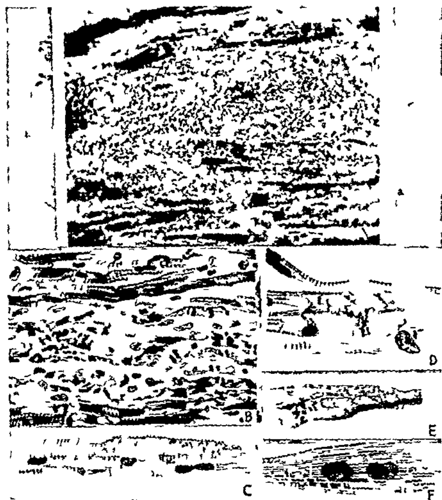


FIG. 16 Acute Chagas Disease myocarditis a) Photograph showing infiltration and dissociation of fibres (Mazza and associates) b) Drawing illustrating principally lesions of the muscle fibres (Torres) c) d) e) f) – As in (b) higher magnification c) Note relative integrity of parasitized fibre d) e) f) Detail of lesions

phages monocytes lymphocytes and some plasma cells *Eosinophiles* may constitute an important percentage of any polymorphonuclears present

Within phagocytes are found erythrocytes cell fragments portions of necrotic muscle fibres and parasites The latter by no means always

demonstrable in inflammatory foci, may be absent in an area with marked changes and present in a nearby region where the tissue appears relatively normal (Fig 16(b)) Giant cells have been observed, these cells contain multiple nuclei, centrally placed[3, 4]

The topography of the lesions can be of more importance than their intensity Pathological changes which involve the intrinsic conductive system do occur it is not known in what incidence, no large series having been encountered but clinical evidence suggests that it is far from infrequent Fatal lesions of this sort may appear quite minor until the significance of their localization is comprehended

In many, perhaps the majority of cases, infiltrate is present not only in the myocardium but also in the endocardial and epicardial layers so that the lesion is actually a pancarditis with myocardial predominance A predominantly perivascular localization of the infiltrate, at least at the outset was observed in experimental studies in animals[11] the cells being first observed around the capillaries and precapillaries, which accompany the fine connective tissue framework of the myocardium, and becoming more marked around these vessels the closer they approach the endocardium In man as the lesion ages sclerotic changes set in marked by progressive fibrosis A type with fibrotic changes from the outset has been described also

The most striking and important abnormality of the muscle fibres is a hyalin degeneration or necrosis In the initial stages the fibres appear enlarged have lost their cross striations and stain strongly with eosin Such fibres as often as not do not contain parasites Later, the fibres rupture retract and form rounded masses or balls which stain intensely black with iron hematoxylin (Fig 16(b)) Such masses may be seen within mononuclear phagocytes[6] Fatty changes usually are not pronounced and are said to be somewhat more prominent in the milder forms[11]

Parasites are found within muscle fibres but are not always directly associated with the above lesions and most often the invaded fibres appear approximately normal a few microns to either side of the parasitic collections It appears as though the mass of micro-organisms had simply displaced the myofibrils causing an enlargement of the fibre at this point but without provoking any disturbance within the same fibre at a distance (Fig 16(c))

The parasitic collections vary in size and in the constituent number of elements Frequently they are large enough to be easily detectable with the low power of the microscope reaching dimensions of 84 by

11 micra[6] In the heart these collections are elongate being limited to one fibre width in breadth The individual elements are the various multiplicative forms the leishmanial type being most frequent Each individual parasite whatever its stage of development contains two structures which when suitably stained are prominent a round nucleus and a rod shaped or rounded kinetoplast (Fig 16(c))

The majority of the parasites are found within the muscle fibres the others occur within phagocytes or are sometimes extracellular They are often abundant in an otherwise almost normal appearing area and absent in regions with pronounced inflammation and necrosis In general tissue forms of *T cruzi* are more numerous during the acute than in the chronic stage

Brain —Inflammatory foci have been found at all levels cerebral hemispheres cerebellum basal nuclei brain stem and spinal cord as well as in the meninges These foci usually small (Fig 17b) are irregularly distributed in both the white and grey matter There is disagreement as to the relationship to blood vessels In the neighborhood of the inflammatory foci Torres[41] finds an infiltration of the adventitium and lymphatic sheath which is obviously connected with the surrounding meningoencephalitis More widespread and not necessarily coinciding with these foci is an endothelial proliferation of the small vessels arterioles and precapillaries which when marked leads to partial or even complete obliteration of the affected vessel Mazza and associates[8] emphasize the perivascular distribution of the infiltrate (Fig 17(a)) and in several cases they were able to trace it along vessels from the meninges into the depth of the white matter Other authors (Vianna[6] Crowell) did not find a direct relation with the blood vessels

Within these foci are parasites proliferated glial cells some plasmocytes and macrophages of vascular and local probably microglial origin[41 4] In the more acute cases polymorphonuclears are present[38] Lesions of nerve cells are not a predominating feature[41] Eventually there is a cicatricial fibrosis of the area[41]

T cruzi usually is intracellular in the brain and has been described within macrophages microglia and neuroglia cells (Fig 17(c)) and with in neurones and vascular endothelial cells[6 41 7] They also appear free but may actually be within the prolongations of glial cells In the focal lesions the micro organisms sometimes are abundant other times absent and then may be found elsewhere in relatively normal appearing tissue

Few reports are available on the chronic type Borges Fortes[12] describes disseminated focal lesions as in the acute type but with fewer



Fig 17 Chagas disease encephalitis a) Diffuse infiltration collections of cells about blood vessels (Mazza and associates) b) Glial nodule (Ash and Spitz) c) Collection of flagellated forms within a neuroglial cell (Vianna)

parasites, in addition there are cicatricial lesions developing at what was apparently the site of such foci He was able to demonstrate T cruzi in one case in which the infection was of more than o years' standing

Other Organs and Tissues — Lymph node lesions are maximal in the satellite node of the early ophthalmic or cutaneous lesion There acute inflammation with minute abscesses necrosis and hemorrhage prolifera tion of endothelial cells in the subcapsular sinuses and large numbers of *T cruzi* are found Other nodes in the same region show similar changes but in lesser degree whereas in distant nodes which become enlarged later, the changes are relatively minor chiefly proliferative and parasites may not be demonstrable [8]

The liver, usually enlarged may show fat within the hepatic cells, in Crowell s case the deposition had a marked periportal predominance A nodular lesion described by Mazza and associates[20] who have encoun tered it in a number of their cases consists of round or oval areas 200 to 500 micra in diameter made up by proliferated histiocytes (Kupffer cells) and sometimes infiltrating cells chiefly monocytes and some lymphocytes Parasites usually are not found in or associated with these lesions

Other organs containing parasites may show pathological change but these usually are not prominent The localization in the thyroid is very uncommon which is of interest in view of the formerly supposed rela tionship to endemic goitre

Skin and eye lesions often absent by the time death occurs have been examined in biopsy material The nodular elements lie under a relatively normal skin the lesion being predominantly subcutaneous and consti tuted of tuberculoid foci with foreign body giant cells large numbers of infiltrating lymphocytes monocytes and fewer polymorphonuclears necrotic fat cells fat laden phagocytic cells and very frequently para sites [9, 28] In the various erythemata parasites often are absent and it has been supposed that they are to some extent allergic phenomena [2, 23, 24]

The early unilateral eye lesion has been studied in some detail in reference to the supposition that it is the earliest lesion and always indi cates the portal of entry Mazza and associates[17] who are not of that opinion state that it is often secondary to generalized blood stream infec tion that the first ocular manifestations are a deep seated orbital cellulitis that this in turn progresses and is manifested by the periocular edema dacryoadenitis and sometimes exophthalmia

Differential Diagnosis of T cruzi in Tissues — Restricted as it is to distinguishing between possible intracellular parasites too much diffi

culty should not be encountered The size and shape are sufficient to exclude metabolic deposits and bacteria With adequately stained preparations both nucleus and kinetoplast will be visible thus eliminating the majority of other possibilities *Toxoplasma*, *Sarcocystis* and *Histoplasma* The chief morphological resemblance is to the various species of *Leishmania*, from which the leishmanial forms of *T cruzi* may be indistinguishable However within any organ, the localization of the two will be different since *T cruzi* is found in the parenchymatous cells (smooth and striped muscle myocardium etc) whereas *Leishmania* almost invariably is not Also flagellated developmental forms of *T cruzi* may be present these are in extreme rarity in leishmaniasis Finally the distribution by organs will be different *Leishmania* infections of the heart and brain being altogether exceptional if they occur at all

Pathogenesis

Precisely how the pathological changes are brought about is unsettled As noted there is often little coincidence between parasites and lesions In the heart for example heavily parasitized fibres can appear approximately normal whereas inflammatory foci may or may not contain *T cruzi* The explanation usually offered is that there is no response to the parasites so long as the muscle fibre is intact, once rupture occurs, an inflammatory reaction takes place part of which involves phagocytosis of parasites and their subsequent destruction or removal from the focus Romaña's experimental studies[9] are not inconsistent with the first half of this view In rats infected percutaneously *T cruzi* multiplies locally within cells for the first 5 days, during which there is no inflammation By the end of this time the parasites mature, leave the cells and the inflammatory phenomena commence This is, of course, an initial local focus of multiplication in a new non immune host, whether the situation is precisely the same in established infections remains to be determined

Torres[11] does not accept the prevailing explanation in toto, at least for the myocardial lesions and insists that the infiltrate is perivascular at the outset and does not start around *T cruzi* either free or intracellular The inflammation is to be related to early vascular lesions and is not a reaction either to destroyed muscular fibres or to the parasites

That certain lesions may develop in the complete absence of any living parasite is suggested by the results of Mazza and associates[60]

Experimental animals were first injected intracutaneously with fractions of killed cultures of *T cruzi* Subsequent intravenous inoculation of the same preparation provoked at the first injection sites cutaneous lesions analogous to those seen in man Accordingly it was concluded that in the human allergic responses may come into play in constituting at least the cutaneous lesions Similar reactions within the myocardium of a few rhesus monkeys have been reported by Muniz and Azevado[61] Killed or lysed organisms were used the preparatory injections being made intravenously and the final one in the cardiac region The lesions obtained were said to reproduce those seen in human cases That the reactions were allergic and not due to toxic substances in the trypanosomes is suggested by the absence of lesions in the controls These authors surmise that a similar mechanism may be active in human cases and that the allergic factor should at least be added to the toxic and mechanical factors producing the lesions

No powerful exogenous toxin has been isolated from *T cruzi* The foreign body reaction seen in the subcutaneous nodules is probably provoked by fatty material freed from lipocytes

Etiology

Characteristics and Description of Parasite

Trypanosoma or *Schizotrypanum cruzi* has very unusual features which distinguish it from other trypanosomes whence its classification by some in a separate genus *Schizotrypanum* Both generic terms are in current and wide use Since the question at issue whether the differences are of generic rank has not been decided upon by the competent body (International Commission on Zoological Nomenclature) *Trypanosoma* is used here not because it is considered more correct but to avoid what may be the temporary use of a term as yet unacclimatized to English For an excellent review of the matter see Dias[6]

The distinctive characters are both morphological and biological *Trypanosoma cruzi* divides not in the blood but in the tissues as an intracellular parasite The process of reproduction is complex and is not accomplished by simple division of the adults but involves the production and subsequent maturation of immature forms which are structurally quite different from the parent blood trypanosome (Fig 18)

In the blood *T cruzi* is a typical trypanosome The kinetoplast

culty should not be encountered. The size and shape are sufficient to exclude metabolic deposits and bacteria. With adequately stained preparations both nucleus and kinetoplast will be visible, thus eliminating the majority of other possibilities: *Toxoplasma*, *Sarcocystis* and *Histoplasma*. The chief morphological resemblance is to the various species of *Leishmania*, from which the leishmanial forms of *T. cruzi* may be indistinguishable. However, within any organ the localization of the two will be different since *T. cruzi* is found in the parenchymatous cells (smooth and striped muscle, myocardium, etc.) whereas *Leishmania* almost invariably is not. Also flagellated developmental forms of *T. cruzi* may be present; these are in extreme rarity in leishmaniasis. Finally, the distribution by organs will be different, *Leishmania* infections of the heart and brain being altogether exceptional if they occur at all.

Pathogenesis

Precisely how the pathological changes are brought about is unsettled. As noted, there is often little coincidence between parasites and lesions. In the heart, for example, heavily parasitized fibres can appear approximately normal, whereas inflammatory foci may or may not contain *T. cruzi*. The explanation usually offered is that there is no response to the parasites so long as the muscle fibre is intact; once rupture occurs an inflammatory reaction takes place, part of which involves phagocytosis of parasites and their subsequent destruction or removal from the focus. Romaña's experimental studies are not inconsistent with the first half of this view. In rats infected percutaneously, *T. cruzi* multiplies locally within cells for the first 5 days, during which there is no inflammation. By the end of this time the parasites mature, leave the cells, and the inflammatory phenomena commence. This is, of course, an initial local focus of multiplication in a new non-immune host; whether the situation is precisely the same in established infections remains to be determined.

Torres[11] does not accept the prevailing explanation in toto, at least for the myocardial lesions, and insists that the infiltrate is perivascular at the outset and does not start around *T. cruzi* either free or intracellular. The inflammation is to be related to early vascular lesions and is not a reaction either to destroyed muscular fibres or to the parasites.

That certain lesions may develop in the complete absence of any living parasite is suggested by the results of Mazza and associates[60]

micra in width is more common early in the infection than later has an elongate nucleus and moves rapidly throughout the microscopic field The wide type is some 4 micra in breadth has a rounded nucleus and while motile is rather ineffectively so displacing itself slowly The shape tends to be rounded, rather like a quarter moon and this appearance is preserved in stained preparations Narrow forms are believed to develop into the wide

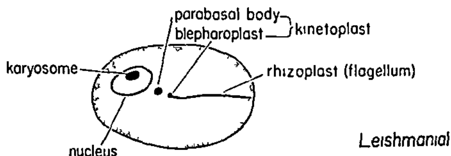
In the tissues *T cruzi* usually is intracellular The leishmanial type is most common this is an ovoid non flagellate body measuring about 4 by micra and containing a nucleus and kinetoplast (Figs 16(c) and 18) It is indistinguishable structurally from a true *Leishmania*, although somewhat larger than most specimens of the latter The aggregates of tissue forms are often referred to as cysts' but there is no evidence of elaboration of a cyst wall

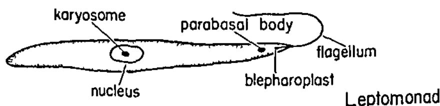
Development of Parasite — The leishmanial forms divide to reproduce themselves Then at a given time they change in structure develop flagella and become elongate (Fig 17(c)) The transformation usually is simultaneous for the members of a single group[3] The final stage in which the aggregates are composed of trypanosomes is encountered rarely possibly it is of very short duration Details of the successive stages are not completely agreed upon Some information on the influence of nutrients and antibodies upon the transformation has been obtained recently[64-66]

The insect phase commences when the blood forms taken up by a suitable host pass into the stomach where crithidial and leishmanial forms are found (Fig 19(a)) These flagellates which mature progress steadily caudad in the midintestine crithidial and leptomonas forms develop from the leishmanias and finally in the rectum the metacyclic infectious trypanosomes occur (Fig 19(b)) in heavy infections to the number of 3 500 per cu mm of feces[9] The cycle requires from one to several weeks The insect once infected remains so for months or even all of its life but the infection is not transmitted to the offspring

Cultivation of Parasite — *T cruzi* grows readily upon blood agar in tissue cultures[67] in the developing chicken egg[8] and will multiply even in citrated guinea pig blood[68] The medium most widely used is N N N blood agar on which cultures incubated at room temperature remain viable for at least one and sometimes many months and are readily maintained by successive subcultures The full range of morphological types may be observed in these cultures While cultures do not always retain original virulence they have been known to contain infective organisms

situated near the posterior end is extremely large often appearing to project beyond the sides of the organism and this is the outstanding morphological peculiarity of the organism (Fig 141) From the kineto plast the flagellum passes anteriorly, attached to the body by a rather narrow undulating membrane with few folds and terminates in a free portion The cytoplasm contains a rounded or elongated nucleus and few chromatic granules





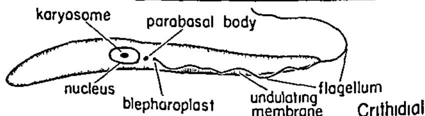


Fig 18 Developmental forms of *Trypanosoma* (Mackie Hunter Worth and associates)

The total length is about 18 micra the body measuring about 11 micra and the free flagellum 7 micra The nucleus is situated somewhat ahead of the midportion of the body approximately at the juncture of the anterior third with the posterior two thirds There are two morpho logical types narrow and wide The narrow trypanosome about 5-30

been maintained for 1 months and blood trypanosomes for 7 months without loss of viability or virulence.[2] No upper limit to this type of storage is as yet known.

Metabolism of Parasite. — *T. cruzi* produced no fermentation nor gas with any of thirteen sugars, although abundant growth was obtained. It was negative in the methyl red and Vosges Proskauer tests and produced no hydrogen sulphide in lead acetate serum agar.[71] Oxygen is consumed by both the culture and blood forms in vitro. This consumption is markedly reduced by potassium cyanide indicating, according to von Brand and Johnson, the presence of an intracellular respiratory enzyme system catalyzed by heavy metals. The thermal death point is 30 minutes at 45 C. and more than 3½ hours at 40 C.[4]

According to M. Lwoff,[6, 7] *T. cruzi* requires hematin, ascorbic acid, one or more factors present in serum and perhaps thiamin. Senekjie[74] did not find ascorbic acid to have much activity. Nicotinic acid, thiamin chloride and pyridoxine promoted growth but in the absence of serum and erythrocytes were unable to maintain it indefinitely.[74] Muniz and Freitas[6] report that nutrient factors are necessary for the progression from one morphological type to another.

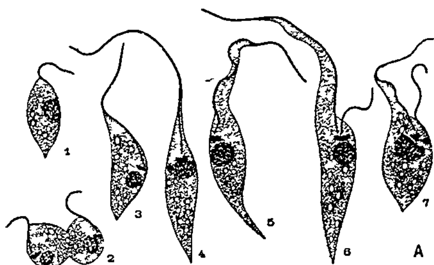
Variants of Parasite. — The range of morphological variation is an important but unsolved question. Biological variants include neurotropic strains said to localize chiefly in the central nervous system and to be rare in the heart. As noted, the regional variations in the severity of the disease have been attributed to the marked variations in virulence.

Immunology

Immunity Prior to Infection

Natural age immunity to acute infections has been demonstrated with laboratory animals. Adult, in contrast to nursling, rats have a lower death rate, a lower peak number of trypanosomes and a shorter period during which trypanosomes are visible in the blood (Kolodny[8]). In a demonstrative experiment a mortality of 98 to 100 per cent was obtained with 20 day old rats and 0 per cent with rats above 40 days.[8] This immunity could not be transmitted passively by injections of serum.

It is not unlikely that a similar age immunity exists in man, and that the large number of fatal cases in infants and children may be so explained. However, it has not yet been clearly shown that in first infections there is a disproportionate number of deaths in the two groups.



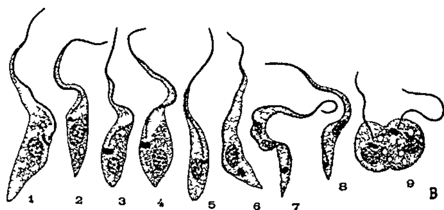


Fig 19 *Trypanosoma cruzi* cycle in the insect a) Leptomonad and crithidial forms from the mid intestine b) Forms from the feces no 8 being the infective metacyclic trypanosome (Brumpt)

after 81 consecutive subcultures in 13 years[3] Recent modifications include the development of a wholly autoclaved medium[9] and from this a liquid autoclaved medium supporting growth at 37 C and suitable for mass cultures[1]

Viability of Parasite — In the frozen state at —70 C cultures have

Thus positive reactions were obtained in 80 per cent of 211 chronic patients means of diagnosis unspecified[11] and in 6 of 9 cases with questionable myocardial involvement[82]

False positives in the complement fixation test are frequent in leishmaniasis, e g, 9 of 11 cases[82] Other so-called false positives obtained in the endemic area are not always easily interpreted In Holland where the disease does not occur 4 of 6 chancroid sera were positive as were 4 of 146 Wassermann positive sera the remainder of 365 samples being negative[83] The incidence of false negatives is not known there is little information of value available In general Wassermann positive sera do not react (Kelser[84, 85]) although the converse is not true, and false Wassermann reactions are reported to be particularly frequent in Chagas disease[86]

Comparison of currently used antigens indicates that the preparation of Davis[19] is preferable because of marked activity stability and absence of anticomplementary power[83, 87] A newer preparation a polysaccharide fraction has shown promise[87]

Precipitin and agglutination reactions are frequently and strongly positive However despite their simplicity, they seem to be less sensitive than complement fixation[81, 83] A precipitin reaction utilizing a water-soluble fraction of *T cruzi*, which does not cross react in leishmaniasis has been described[88] and may prove to have certain advantages for diagnostic use

Allergic Phenomena — The possible importance of spontaneous allergic manifestations in the genesis of the pathology has been considered Such reactions also have been consciously utilized in an attempt to develop a diagnostic skin test Meyer and Pifano[89] described a marked reaction in patients to the intradermal injection of killed *T cruzi* Muniz and Freitas[87] could not confirm these results whereas Mazza and associates did obtain skin reactions in patients as did Romaña and Cossio[91] but in only 8 of 12 patients In the latter series some patients gave a positive skin test when the complement fixation reaction was negative In immunized rabbits Senekjie[92] obtained marked responses It seems that the method is promising but cannot yet be used for diagnostic purposes

Treatment

The therapy of Chagas disease is not satisfactory Tryparsamide antrypol atoxyl antimony compounds and the arsphenamines are of no

Comparison of mortality rates of the two groups in endemic areas is not sufficient since the possibility that the adults are the survivors of a childhood infection has not been eliminated. A satisfactory group would consist of adult immigrants to the endemic area and no report on the mortality of such a group has been encountered.

Immunity During Infection

T. cruzi infection is very long lasting. It is known to persist for at least 14 years as Dias has shown in two hospitalized patients for whom the possibility of reinfection seems most unlikely.[illegible] During the infection immunological phenomena are marked but it is not known that the immunity is ever adequate to sterilize. The coexistence of immunity and continued infection has led to the supposition that the immunity is of the "premunition" type, *i.e.* immediately dependent upon the infection and ceasing with it. The latter point has not been demonstrated.

In infected animals there is a resistance to reinfection and in natural human infections a development of antibodies and reactions of an allergic type.

Resistance to Inoculation. — Rats recovered from an initial infection and no longer showing trypanosomes in the blood did not have a visible blood infection when reinoculated. Their sera contained antibodies which acted both prophylactically and therapeutically in normal animals (Culbertson and associates[80]). Immune bodies are also present in the milk of lactating infected rats and are transmitted to the sucklings.[8]

Antibody Formation. — In man antibodies are produced which fix complement and produce agglutination and precipitation reactions in the presence of the specific antigen.

The general interpretation of the complement fixation test, already given, depends upon the following data. In rhesus monkeys experimentally infected fixation was obtained 5 days after infection and before parasites appeared in the blood; thereafter titres rose to reach 1:1,280 or higher by the tenth day and remained high until death (Muniz and Freitas[81]). In man, when infection was proved by some other method the test has rarely been negative, e.g. Romaña and Dias[8] who obtained fixation in 25 of 26 such cases. Of proved cases in the chronic phase 13 of 14 had reacting sera although sometimes of very low titres.[83] It is when other methods fail that the test could be of the greatest value. Unfortunately its significance in such instances is not altogether clear.

them S1544, S1577 and S1582 are stated to have significant therapeutic action[7], the first two being about as active as 7602 (Browning, Calver and colleagues[39]). S1544 is 3 carbethoxyamino-9 p carbethoxyamino-phenyl 10 methylphenanthridium chloride; S1577 is the corresponding methane sulphonate and S158 is 2, 7 dicarbethoxyamino 9 10 dimethylphenanthridium metho sulphonate.

Since *penicillin* has been reported on enthusiastically but inadequately, it may be noted that in laboratory experiments it has proved inactive[9,190]. There is no reason to believe that the favorable effects cited in two reports, each with one case, were more than coincidental[1,191], and in another case such favorable action was not observed (Talice[190]).

Supportive and Cardiac Therapy — Bed rest is advised during the acute period to reduce strain on the heart. When there is myocardial involvement but no insufficiency, violent physical exercise is prohibited but in so far as possible the habitual activity is not interfered with[18]. Quinidine is advised for ventricular extra systoles; for partial auriculo ventricular block with vertigo, atropine has been helpful[18].

When the stage of marked insufficiency is reached, bed rest is indicated. Effusions when present may be reduced by withdrawal of fluid. Edemas usually will regress with mercurial diuretics combined with salt suppression and restricted liquid intake; if not, there may be hypoproteinemia, and a protein rich diet is recommended. Cardiotherapy with digitalis or strophantus is said to do more harm than good. If used at all these drugs should be employed with great caution, employing small initial doses and carefully following the response to gradual increases[18].

Transmission

Chagas' disease is almost invariably contracted by contact with the natural arthropod vector, the triatomas, other mechanisms playing a distinctly secondary role.

Arthropod Transmission

Triatomas — Mechanism of Transmission — Trypanosomes rarely if ever occur in the salivary glands and the bite is non infective in almost every instance. It is the feces of the vector which contain the infective

value in this condition[93] Recently two types of compound known to have anti trypanosomal action have been developed but remain to be accurately evaluated

Antiparasitic Therapy — "7602 Ac" was introduced as a secret proprietary According to the British Intelligence Report it is diallylmalondi (4 amino-2 methyl quinolyl 6 amide)[94], and descriptions and formulae published prior to 1946 are incorrect or incomplete (Curd[94]) A British product said to correspond, is called M3024 Fulton[5] reported that maximum tolerated doses did not sterilize infected mice but would produce temporary negative periods According to Mazza who cites the manufacturer the drug is inactive against the tissue forms[9, 96]

It is given intramuscularly as a water solution, usually at 3 per cent, sometimes at 1 5 per cent strength[18, 38] Single 5 c c doses (150 mgm) are usual but up to 8 c c (240 mgm) have been given to nurslings The injections usually are given daily or every other day Mazza[38, 47] recommends the following total doses (a) Nurslings particularly with encephalitic symptoms up to 100 mgm /kg as rapidly as possible', then if renal tolerance permits go on to 200 mgm, (b) in young children give 60 to 100 mgm (c) at other ages 30 to 60 mgm

The injections cause a certain amount of pain which may be sufficiently marked to require use of a local anesthetic[6] Usually there is a febrile reaction later in the day on which the injection is given In some cases urinary albumin appears, 7602 is then stopped, the albumin usually diminishes spontaneously and when treatment is resumed, does not reappear[97]

The degree of value of the drug cannot be established on the basis of present information Mazza and collaborators[9] have used it in over 100 cases and report an immediate beneficial action, the fever is lowered the general symptoms improve and the skin manifestations regress rapidly In three meningoencephalitic cases recovery is attributed to its use[38] although study of the records shows that in two of the three chemotherapy was initiated at a time when unfavorable cases had died Parasitic relapses have been noted after use of the recommended doses

The use of 760 seems warranted at present in the absence of other available treatment and since the toxicity is apparently low Temporary improvement is it would seem the most which can be expected With the doses which have been used relapses are to be anticipated and it is not to be presumed that the infection can be eradicated with this product

Phenanthridium Compounds — At the time of writing these compounds have not yet passed beyond the experimental stage but three of

found naturally infected[19] In South America *Triatoma infestans*, *T* *(Eutriatoma) sordida* and *Rhodnius (Panstrongylus) megistus* are important vectors The triatominae have in successive years been subclassified in an ever increasing number of genera Older well established names having been preferred in this article the generic terms used have

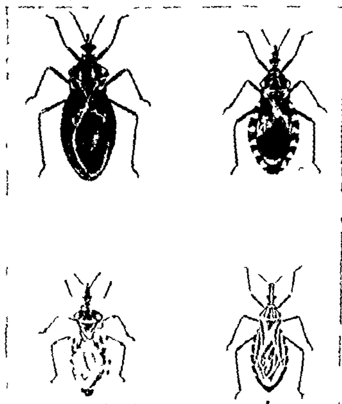


Fig 20 Principal vectors of Chagas disease 1 *Panstrongylus megistus* 2 *Triatoma infestans* 3 *Triatoma sordida* 4 *Rhodnius prolixus* The scale to the right side of each insect is about ⅙ natural size (Dias and associates)

various synonyms of which the more common are indicated Natural infections have been reported for the following genera *Triatoma Eratyrus, Rhodnius, Panstrongylus, Eutriatoma, Meprata, Dipetalogaster Mestor, Parabelminus* and possibly *Psammolestes* and *Cavernicola*[14, 0, 105]

The triatomas are striking insects large and often brightly colored (Fig 20) Adults are winged the immature stages which otherwise

metacyclic trypanosomes (Fig 19(b)) Since these are not inoculated, they are probably introduced into the bite wound by scratching or into the eye or elsewhere There is some capacity to traverse the normal skin Although in man experiments have given negative results , infection has been so obtained in animals Rates ranging from 0 to 80 per cent have been thought to depend chiefly upon the rate of desiccation [illegible]

Description — The triatomas or *Triatominae* are large winged insects predominantly American in distribution They are all blood sucking hemiptera of the family *Reduviidae* In the United States they are popularly known as Mexican or China bedbugs assassin bugs, cross bugs (from the crossed position of the wings) or kissing bugs (because of their frequent fixation about the mouth for blood sucking) Popular synonyms used in South America are in Brazil barbeiro chupão or chupança in Argentina Chile, Bolivia vinchuca, in Colombia, Venezuela pito or chipo

Of the some 72 known species of triatomas, very nearly all are found in the Americas where they are distributed from 46 south latitude (Mazza and collaborators[1]) to about 41 north in the United States (data of Usinger[20]) A few species are described from Africa, Asia, Oceania, one *(Triatoma rubrofasciata)* is cosmopolitan

About half of the American species have been found spontaneously infected Of the remainder all experimentally tested have also been infected these now number about 19 additional species[9] The incidence of natural infection in the same species varies from 0 to 80 or 100 per cent according to the hosts fed upon These rates are often highest in house-inhabiting species in the endemic regions The importance of any given species lies chiefly in the closeness of its association with man

In the United States 7 naturally infected species all belonging to the genus *Triatoma* have been found by Kofoid and collaborators S F and F D Wood Packchanian and Davis and associates [20, 104] They are *T gerstaeckeri T lecticularius T longipes, T protracta, T rubida, T sanguisuga* and *T ambigua T heidemanni*, sometimes referred to, is *T lectularius*[20]

The incidence of infection has ranged from 20 to 9- per cent according to the species and locality [9] The known distribution of the infection is Southern California Arizona New Mexico and Texas It seems probable that eventually it will be found throughout a much greater area since according to Usinger[20] the distribution of vector species is from coast to coast throughout the southern half of the United States

In Panama *T (Panstrongylus) geniculata* and *T dimidiata* have been

areas have been experimentally infected and have served as vectors under laboratory conditions Thus *Amblyomma longyrostre* has been found naturally infected and to contain in its feces trypanosomes infectious for laboratory animals Experimental transmissions from animal to animal have been achieved with *A cayennense* and *Rhipicephalus sanguineus* (Pifano[1 8]) Among the soft ticks the following ten species of *Ornithodoros* have been successfully infected *O moubata*, *O coniceps* *O laborensis* *O rugonei* *O nicollei* *O rostratus* *O tholozani* *O savignyi*, *O turicata*, *O venezuelensis*[109] Finally in both species of human bedbug *Cimex lectularius* and *C rotundatus* infections develop[109] as they do in a variety of insects which do not feed on man

Nonarthropod Transmission

Parental transmission to the offspring is believed to occur and has been observed in animals. Two possible mechanisms have been envisaged Congenital transmission was suggested by C Chagas in his early studies nervous manifestations in new born infants suggesting acquisition in utero[29] Also the disease might be acquired post natally during suckling Mazza cites an indecisive although possible instance A child born to a woman with symptoms of Chagas disease had when ten days old a blood examination which was negative The mother and child then left the endemic area At 11 weeks of age *T cruzi* was found in the blood of the child and in the milk but not in the blood of the mother Six days later the mother s blood was again negative[28 109] The nodular cheek lesions of suckling children may be significant in this respect it is universally agreed that the trypanosomes can traverse the mucosae

The incidence of parentally contracted infection is not known if as suggested[28] it accounts for all the cases in which the infants show no obvious sign of external origin of the infection then this source is more important than had been realized Data from animal experiments are complementary and suggestive Both of the above mechanisms occur *T cruzi* passes into the milk with great regularity (Nattan Larrier[110]) and is readily infective by the oral route[111] Infections in utero occasionally take place and may be followed by death of the fetus The abortion rate in the infected pregnant female was very high[11]

Direct transmission by contact is rare It may be responsible for some cases in persons who deal with infected animals either through the prep aration of animals for their pelts or for culinary purposes Conceivably

resemble the adults in general appearance, apterous. All stages and both sexes are hematophagous, and since the *T. cruzi* infection, once acquired, is transmitted from stage to stage, both nymphae and adults are possible vectors. In nature they are predominantly nocturnal feeders but in the laboratory will feed at any time. Their bite usually is painless. They feed by preference upon mammals but will utilize birds and even cold-blooded animals. They are hardy, and adults of some species resist starvation and desiccation for a year or longer. The female begins to deposit eggs some two weeks after copulation and may eventually lay over 200 which are deposited either at random or, in certain species, are fixed to supports. Five moults are undergone before reaching maturity and the complete life cycle requires 3 to 15 months according to the species and environmental circumstances. In nature most species have one annual generation.

Wild and domestic species are distinguished, the latter being of greater importance in transmission of the human disease, the former serving to maintain the wild animal reservoir. The domiciliary species have the habits of bedbugs; they hide in the crevices of walls or in the bed, emerging after the lights are extinguished, feed with rapidity and regain their lairs. In endemic areas they can be extremely abundant; 000 have been recovered from a single wattled hut and over 14 000 from 13 houses[106]. Wild species often are found in nests or bedding of animals.

Triatomas are most frequent and active in the warmer periods of the year in regions with definite seasons; these fluctuations are less marked where it is continually hot. Although apparently preferring tropical conditions they survive and retain their infections at temperatures below 0° C, as in Rio Grande do Sul, Brazil[107], and may be encountered at 6 000 feet elevation[61]. In general the triatomas are, like their relative the bedbug, highly adaptable in regard to habitat, and it appears that they are adapting themselves more and more to life in human habitations, now for example occasionally being found in concrete buildings. There is some evidence that present heavily infested areas have become so within the last 100 years, and one author believes that triatomas became important human feeders only in recent historic times, the decisive favoring factor being the present type house which became popular after the conquest of the Americas by the Europeans.

Other Arthropods.—Epidemiologically only the triatomas are known to be of any importance. However, *T. cruzi* has been found in at least one species of tick, other ticks, some prevalent in the endemic

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or absent. Higher temperatures probably act by favoring the abundance and activity of the insects; the cold may also have a direct adverse effect since many insects are said to lose their infection during the cold weather.[8]

Animal Reservoir

No less than 38 species of animals have been found naturally infected,[4] including such diverse groups as monkeys, cats, dogs, foxes, squirrels, ferrets, opossums, armadillos, ant eaters, porcupines, mice, rats and pigs, and experimental infections have been established in chimpanzees, baboons, dormice, hedgehogs, sheep and goats as well as in the ordinary laboratory animals. Information on the species of wild animals involved may be found in Pinto,[5] Usinger[6] and Talice.[7] Bats frequently carry trypanosomes akin to, but not proved to be identical with, *T. cruzi*[113] four species having been found in the United States.[6, 116] In general birds and reptiles are not susceptible.

Amongst the domestic animals important reservoirs are dogs and cats. Gasic[11] in Chile found infections in 0.4 per cent of 184 dogs and 4.4 per cent of 136 cats. Of the wild animals, armadillos particularly are often found to carry *T. cruzi* and in Brazil some 40 per cent of certain species are carriers.[4] In the United States natural infections have been found in the following: armadillos (*Dasypus novemcinctus texanus*), house mice, the opossum (*Didelphis virginiana*) and several species of the wood rat *Neotoma*.[6]

Insect Vectors

The triatomas are of importance in the man to man cycle, in the transfer of trypanosomes from animals to man and in the passage of the infection between animals. In human disease the importance of any given triatoma lies in its habitat: triatomas living in houses are immediately dangerous, the others less so, and it has been shown that in a given area there may be infected animals and infected vectors but few or no human cases if the sleeping quarters are not infested. Even the same species found in a single group of buildings may show great variation, with a high rate of infection in those taken in dwellings and no infection at all in specimens collected in outbuildings such as the hen house, e.g., *T. infestans*, Pinto.[5]

there may also be a food source, either through contamination of ingesta or by consumption of insufficiently cooked meats

Epidemiology

Perpetuation of the infection requires passage back and forth between insect and mammal for so far as is known, direct transmission does not occur frequently enough in either of these hosts to assure indefinite maintenance In the endemic areas *T cruzi* is found in man the insect vectors and in wild and domestic animals

All races both sexes and all ages are affected Younger age groups predominate among acute phase patients This may signify chiefly that recent arrivals in endemic areas are quickly infected, although children are perhaps more exposed and when nursing are open to an additional source of infection In the chronic phase an increased number of older persons are represented but even then they do not predominate, in 90 cases of chronic cardiopathy 40 per cent were in the age group 6 to 20 and 30 per cent were aged 21 to 40[18] In overall statistics, where the acute form is probably weighted because it is more readily recognized about one third of 254 cases were in the group up to 10 years, another one-third were 10 to 20 years old the remaining one-third being distributed over subsequent decades with a small but distinct drop in incidence in each ten year period[113] The higher incidence in infants and young children of hyperacute forms which end fatally, may perhaps be related to the data on increasing resistance with age obtained in animals

Chagas disease is contracted at home in bed at night and in the dark Consequently occupations are not of primary importance although hunters for example may be exposed to more sources of infection than the general population The disease is most prevalent among poorer persons the simple type of dwelling inhabited being favorable to the triatomas

The disease is primarily rural or suburban Urban distribution although most unusual cannot be considered an impossibility, Guimarães and associates[114] having described a potential focus in the center of Rio de Janeiro where in a park infected animals and vectors were established the latter having also been taken in nearby buildings Triatomas may be found in modern concrete structures[114, 102]

Seasonal variation in cases is marked in temperate climates Mazza[17] in Mendoza Argentina observed 94 per cent of his cases from November through April with the peak in March In warmer regions with less fluctuation of temperature monthly case variations may be less marked

Insecticides and Fumigants

Equivocal results have been obtained with D D T (dichlorodiphenyltrichlorethane) Lent and Oliviera[119] used a 5 per cent preparation combined with talc against *Panstrongylus megistus*, *Triatoma sordida* and *T infestans* They found the action slow particularly against the immature stages After 18 to 24 hours of exposure most of the insects began to be affected but recovery still was possible Eggs of *Rhodnius prolixus* hatched after 10 days of exposure in a treated dish Other trials using pure crystalline D D T did not show increased rapidity of action over the 5 per cent strength Similar results were reported by Dias[18, 106] using the commercial gesarol in strengths up to 10 per cent Randolph[1] used a spray preparation and reported 100 per cent mortality of the Texas *T lecticularius occulta* The insects were confined to small cages the walls of which had been sprayed previously One to 5 per cent D D T sprays killed all specimens in periods up to 8 days the 5 per cent strength giving a 100 per cent kill in 3 days Unfortunately the final concentration on the wall is not given so that it is not known whether the concentrations achieved are practical for field use It seems apparent that the whole matter needs more detailed study

Pyrethrum base insecticides applied in sprays or mists are said to be effective after use many insects flee the building rapidly but then die however the preparations tested had neither residual action nor ovicidal action so that reapplication every three to four weeks was recommended[18, 106] Trials with gammexane containing as an active ingredient the gamma isomer of benzene hexachloride have in the brief initial reports given favorable results and gammexane sprays and pyrethrum powders are considered the best of the available products[121] Talice[9] reported on fumigants sulfurous anhydride (SO_2 gas) causes triatomas to leave a building whereas hydrogen cyanide will kill them within 10 minutes

Insecticidal measures should be combined with an attempt to eliminate favorable hiding and breeding places and to prevent ingress from the exterior Since the poorer type house may have wide cracks in the floors and walls and a thatched roof attempts to insect proof may be impractical and it may prove preferable to abandon the infested houses and build new ones[18] The best type of construction is not agreed upon but a minimum aim should be to have floors walls the roof and ceilings tight Screens are of value to prevent entry of triatomas from neighbor

A factor to which Brumpt particularly has drawn attention is the rapidity with which the insects defecate. Those such as *T. (Panstrongylus) megista* and *R. prolixus*, which pass feces toward the end of the blood meal while still on their host, are more effective transmitters than *T. protracta*, for example, which evacuates much later.[3]

In South America *Triatoma (Panstrongylus) megista*, *T. sordida*, *T. infestans* and *Rhodnius prolixus* are of great importance in human infections. *T. (Panstrongylus) geniculata* maintains infections between armadillos but has been taken in houses. In the United States all common species have been found in association with wood rat (*Neotoma*) nests.[9] *T. heidemanni* (= *lecticularius*) has been taken also in houses and from bedding.[10]

Natural infection rates are high in comparison to other protozoan diseases such as African trypanosomiasis or malaria. They will vary somewhat according to locale and are highest in domestic species in the endemic region or when taken from nests or burrows of infected animals. Talice[9] gives the results of the following South American surveys:

T. infestans	Uruguay	39 per cent of 729 infected
R. prolixus	Venezuela	80 per cent of 1 680 infected
T. infestans	Argentina	16.5 per cent of 30 865 infected

Mazzotti found 8 per cent of 1 402 Mexican specimens of various species infected. In the United States rates have varied from 20 per cent of 957 *T. protracta*[19] to 9 per cent of 100 *T. gerstaeckeri*.[21] This difference in rates more probably reflects association with infected hosts than particular suitability to *T. cruzi*.

Control

This major practical problem has received attention only in recent years and the data bearing upon it are still so fragmentary that little can be said which is precise. There is no effective vaccine and experiments in this direction thus far have been distinctly unpromising.[114] Therapy cannot be relied upon to sterilize the infection so that it is not feasible if even possible to eliminate the human source of infection.

Accordingly the measures proposed have attacked the man-vector link in the epidemiological cycle and have involved insect eradication and prevention of access of triatomas to man.

Insecticides and Fumigants

Equivocal results have been obtained with D D T (dichlorodiphenyltrichlorethane) Lent and Oliveira[119] used a 5 per cent preparation combined with talc against *Panstrongylus megistus, Triatoma sordida* and *T infestans* They found the action slow particularly against the immature stages After 18 to 24 hours of exposure most of the insects began to be affected but recovery still was possible Eggs of *Rhodnius prolixus* hatched after 20 days of exposure in a treated dish Other trials using pure crystalline D D T did not show increased rapidity of action over the 5 per cent strength Similar results were reported by Dias[18 106] using the commercial gesarol in strengths up to 10 per cent Randolph[?] used a spray preparation and reported 100 per cent mortality of the Texas *T lecticularius occulta* The insects were confined to small cages the walls of which had been sprayed previously One to 5 per cent D D T sprays killed all specimens in periods up to 8 days the 5 per cent strength giving a 100 per cent kill in 3 days Unfortunately the final concentration on the wall is not given so that it is not known whether the concentrations achieved are practical for field use It seems apparent that the whole matter needs more detailed study

Pyrethrum base insecticides applied in sprays or mists are said to be effective, after use many insects flee the building rapidly but then die however the preparations tested had neither residual action nor ovicidal action so that reapplication every three to four weeks was recommended[18 106] Trials with gammexane containing as an active ingredient the gamma isomer of benzene hexachloride have in the brief initial reports given favorable results and gammexane sprays and pyrethrum powders are considered the best of the available products[1 1] Talice[9] reported on fumigants sulfurous anhydride (SO gas) causes triatomas to leave a building whereas hydrogen cyanide will kill them within 10 minutes

Insecticidal measures should be combined with an attempt to eliminate favorable hiding and breeding places and to prevent ingress from the exterior Since the poorer type house may have wide cracks in the floors and walls and a thatched roof attempts to insect proof may be impractical and it may prove preferable to abandon the infested houses and build new ones[18] The best type of construction is not agreed upon but a minimum aim should be to have floors walls the roof and ceilings tight Screens are of value to prevent entry of triatomas from neighbor-

A factor to which Brumpt particularly has drawn attention is the rapidity with which the insects defecate. Those such as *T. (Panstrongylus) megista* and *R. prolixus*, which pass feces toward the end of the blood meal while still on their host, are more effective transmitters than *T. protracta*, for example, which evacuates much later.[3]

In South America *Triatoma (Panstrongylus) megista*, *T. sordida*, *T. infestans* and *Rhodnius prolixus* are of great importance in human infections. *T. (Panstrongylus) geniculata* maintains infections between armadillos but has been taken in houses. In the United States all common species have been found in association with wood rat (*Neotoma*) nests.[9] *T. heidemanni* (= *lecticularius*) has been taken also in houses and from bedding.[10]

Natural infection rates are high in comparison to other protozoan diseases such as African trypanosomiasis or malaria. They will vary somewhat according to locale and are highest in domestic species in the endemic region or when taken from nests or burrows of infected animals. Talice[9] gives the results of the following South American surveys:

T. infestans	Uruguay	59 per cent of 7 9 infected
R. prolixus	Venezuela	80 per cent of 1 680 infected
T. infestans	Argentina	16 5 per cent of 30 865 infected

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Control

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ing hen houses or other animal quarters? Within the house beds and beddings should be made as free from hiding places as possible and sprayed frequently, the reed mat bedding frequently used in endemic areas is *particularly objectionable* Cats and more particularly dogs frequently are infected, when found to be carriers they should be disposed of

Individual prophylaxis in an endemic area involves the avoidance of infected habitations so far as possible Houses of some age constructed of wood or adobe with wide cracks in floors and walls and with thatched roofs are particularly dangerous Bed nets have proved effective[18], they will exclude adults but unless of unusually fine mesh, not the immature stages[105] They may be used with a transported bed or hammock, otherwise *it may prove prudent to spray the bed before installing the net* The value of repellents is not established

It seems evident from the foregoing that present procedures of control are not altogether satisfactory There is need for efficient inexpensive long lasting measures towards the discovery and application of which attention should be directed

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CHAPTER XXXVI

LEISHMANIASIS

By S. LYLE CUMMINS

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KALA AZAR AND ALLIED LEISHMANIA DISEASES

INTRODUCTION

Kala azar (black fever) first attracted attention in 188- as the result of a report by McNaught[1] on an epidemic disease prevalent in the Garo Hills in Assam Although at first thought to be chronic malaria, it was declared by successive investigators to be ankylostomiasis, then again malaria and finally malta fever It was not until Leishman, working at Netley detected peculiar bodies in the spleens of soldiers invalided from India as cases of chronic malaria (1900) and, recognizing the similarity of the nuclear arrangement to that in trypanosomiasis, published in 1903 in the British Medical Journal a note On the Possibility of the Occurrence of Trypanosomiasis in India that the true nature of kala azar was recognized and Leishman bodies' were proved by Donovan[2] (who had found them independently just before Leishman's publication) Bentley Leonard Rogers and others to be the causative organism of the disease

In 1904 Rogers[4] succeeded in cultivating the parasites in their flagellate form and demonstrated that the organism was not, strictly speaking a trypanosome but a herpetomonad with a terminal flagellum instead of an undulating membrane The name *Leishmania donovani* was given to the parasites of kala azar and the group came to be called *Leishmania* Rogers' work pointed strongly to a development of the round Leishman body to a flagellate in some insect host and Patton[5] in 1907 obtained the complete development of the parasite in bed bugs (*Cimex rotundatus* and *Cimex lectularius*)

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the Sudan (Neave[6] Cummins), and in Tunis (Catheire and Nicolle) while Nicolle[8] in 1908 called attention to the fact that in North Africa the disease tended to affect infants rather than adults He also showed that it was possible to infect dogs and monkeys by intraperitoneal inoculation of spleen juice from human cases and demonstrated the existence of a natural kala azar in dogs[9] in North Africa

In Italy Basile[10] and others proved that both infantile and canine kala azar were common and an investigation was carried out tending to show that the disease might be carried by fleas Bousfield[11] Marshall and Archibald[12] working in the Sudan added knowledge, and the two latter workers infected monkeys by inoculation by contact and by feeding

Parallel investigations were carried out on oriental sore a contagious disease proved by Wright[14] of Boston to be due to a *Leishmania* parasite All light thrown on each of these separate but very similar diseases has helped to illustrate the other Finally a mucocutaneous disease known as 'espundia' or 'buba' has been proved to be caused by a *Leishmania* parasite morphologically similar to those already mentioned All recent work has been directed to sand flies as vectors not only for kala azar and for *Leishmania tropica*, as the cutaneous ulcer is called but also for espundia

GENERAL CONSIDERATION OF THE LEISHMANIA GROUP OF PARASITES

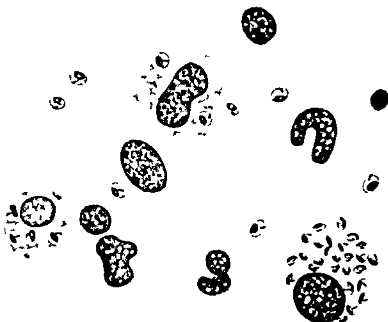
As careful study has failed to discover any morphological character by which to differentiate the *Leishmania donovani* of India kala azar from the *Leishmania infantum* of the Mediterranean or from the parasite of oriental sore or of espundia either in the aflagellate or the flagellate stages the following description may be taken to apply to the whole group

Aflagellate Stage of Leishmania

The parasites are round or oval often slightly pointed at one end tending to resemble oat grains in shape from 2 to 4 micra in breadth (Figs 1, and 9) Their shape is well maintained even after the manipulations involved in filming They appear to be intracellular but are



L I St Kalı ızar Film from spleen × 1000 d m



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C tc f D ı f ll C d C ll ı Kla t
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L. Rogers[1] in 1904 succeeded in cultivating them by adding material obtained by spleen puncture from Indian cases of kala azar to about 1 c.c. of sterile salt solution containing a little sodium citrate to prevent clotting and kept at 22°C. The medium found best suited for the Mediterranean form of the parasite and now found to be applicable for general use is that of Novy, MacNeal and Nicolle, the NNN medium, of which the formula, as given by Manson-Bahr,[8] is as follows: 'Dissolve 14 grams agar and 6 grams sodium chloride in 900 c.c. of distilled water; steam for two hours; filter through cotton wool; distribute 3 c.c. per test tube and autoclave at 102°C for 20 minutes. Cool to 55°C and add to each tube 20 drops of sterile whole rabbit's blood; mix thoroughly; slope the tubes; incubate for sterility test and to sweat. Suspected material is inoculated into water of condensation. Cultures are incubated at 22°C. Developmental forms are found in positive cases in from 4 to 5 days and up to 10 days.'



Fig. 3. "Rosette" of flagellate form from culture from a case of kala azar, magnification 1,000 diameters; preparation lent by Sir W. B. Leishman.

We must now turn to the consideration of the relationships and the

often found outside cells in films owing to bursting of the containing envelope of the macrophage while making the spread Colored by Leishman's stain or any variety of Romanowsky staining (Fig 1) the cytoplasm takes a clear blue tint and in young and healthy parasites usually is free from vacuoles or granules The nuclear apparatus consists of a larger spherical macro- or tropho nucleus tending to be closely approximated to the cell membrane and a smaller micro or kineto nucleus often rod-shaped and taking the stain more intensely, thus contrasting sharply with the less intensely stained macronucleus



Fig Leishman Donovan bodies in large mononuclear cell smear preparation magnification 1 000 diameters

Flagellate Stage of Leishmania

The aflagellate stage of the parasite in material obtained from a case of kala azar by puncture during life of spleen, lymph node bone marrow or liver or obtained by early post-mortem examination, if placed in a suitable medium and at a favorable temperature develops into flagellate forms (Fig 3) comparable in every respect with the class of parasitic protozoa called *Herpetomonads* The fully developed flagellum is from 15 to 20 micra in length and the parasite from 1 2 to 2 micra in width, and the organism moves with the flagellum forward Rosettes (Fig 3) consisting of young flagellates with the flagella pointed towards the centre of the group are produced by the rapid division of the parasites

a disease being at that time described in India It was not until Leishman[2], working at Netley in 1900 on spleen smears from soldiers invalided from India as chronic malaria , recognized the similarity of the nuclear arrangement of the parasite to that of trypanosomiasis and published in 1903 in the British Medical Journal a note on the possibility of trypanosomiasis in India that Leishman s bodies were recognized as the cause of kala azar This was confirmed independently by Donovan[3] who had found them just before Leishmans publication but three years after Leishman had discovered them Soon they were recognized by L Rogers[4], Gentley and others The remainder of the history of this parasite in its flagellate phase has been described already in an earlier section of this chapter It soon came to be known as the Leishman Donovan body thus recording both the discoverers by name

Rogers work pointed strongly to the probability of an insect host The low temperature at which the cultures were successful was very much in favor of this and Patton[35] in 1907 obtained development from the spherical form up to the flagellate in the bed bugs *Cimex rotundatus* and *Cimex lectularius* This result however appears to have no great importance in the history of the disease except to show that an insect temperature is favorable to the formation of flagellates as the parasite does not advance to the proboscis and the distribution of the bed bug does not correspond to that of kala azar As Napier[18] says Many thousands of bed bugs which have been caught in the houses and actually in the beds of kala azar patients have been dissected from time to time but none of these has ever shown a Leishmania infection In the same category must be put also the many mosquitoes ticks mites and animals of a higher creation such as leeches which have been tried from time to time Until Wenyon[36] called attention to the sand fly in a short note on oriental sore progress seemed to be at a stand still

Geographical Distribution

Kala azar first noted in Assam although misunderstood as to its causative organism was at that time in its epidemic phase at the foot of the Garo Hills and up the Brahmaputra Valley It was almost confined to the low lying parts of east India chiefly to the country districts but also to some of the great towns like Calcutta and along the Ganges (Fig 4) It is remarkable how kala azar has always been confined or

differences between (1) the leishmania group of diseases known as kala azar causing visceral disease, (2) the invariably localized form caused by *Leishmania tropica* and (3) espundia, ordinarily localized but liable to mucocutaneous lesions as well, following the local lesion much as generalized syphilis follows a chancre To do so we shall study each in turn

KALA AZAR

Kala azar (synonyms, visceral leishmaniasis, dum-dum fever, tropical splenomegaly, etc), which is a visceral disease, has tended to be split up on geographical and other grounds into Indian or Asiatic Leishmania African Leishmania, Mediterranean Leishmania or *Leishmania infantum* and American Leishmania or Chagas' disease It seems probable that the American form of kala azar, however, has been introduced from Europe or from Africa, and as to the others, there seems no good reason to distinguish between them, and we propose to treat of them all as the same

History

The first form of kala azar to be described, but of course without any reference to the parasite, was the "black fever" described by McNaught[1] in 1882 in the Garo Hills of Assam This same fever was reported on again by G M Giles in 1890[15], he regarded it as a form of ankylostomiasis and called attention to it as depopulating certain areas at the foot of the Garo Hills It was known as "black fever" among the Garos because of a change of color to a deep brown or black noticed in many of the cases The disease was characterized by marked splenomegaly enlargement of the liver and, in many cases, by cancrum oris and often by extreme wasting, anemia and edema of the lower limbs In 1896 97 L Rogers[16] investigated it, noting a terrible outbreak in Nowgong in Assam and showing that so appalling and so fatal was the disease when it struck at virgin soil, that there had been a 31 5 per cent decline in the population in the decade 1890 to 1900 Although he made the not unnatural error of regarding the outbreak as a very severe form of epidemic malaria an opinion which Ross in 1899 shared he noted the remarkably high incidence of the disease and its dreadful mortality, an incidence and mortality, we may say, seldom seen in India

Bentley in 1902 considered the disease not malaria but Malta fever,

almost confined to the east of India, thus differing from the almost completely localized type caused by *L tropica*, which is commonest towards the dusty and rocky districts of the west and north In its endemic form it is common in the southern Sylhet valley of Assam in lower Bengal Bihar in the United and Central Provinces and in Madras City The areas affected have in common a considerable humidity a minimum mean temperature of not below 50°F and an elevation not above a height of 2,000 feet Apart from India it is prevalent in an area of the Sudan about the river basins of the Blue Nile and the Rahad (Fig 5) In China it prevails from Peking in the north to the Yangtsi Kiang River It is found in Russia and in Turkey The so called infantile type' which is not however confined entirely to infants is chiefly a disease of the Mediterranean basin (Fig 6) The American form of the disease probably introduced from India the Mediterranean basin or Africa is said to be spreading fast in Brazil and other countries and is likely to attract a great deal of attention in the near future

Epidemiology

In the epidemiology of kala azar two elements have to be taken into account circumstances bearing on the human stock and those bearing upon the distribution and prevalence of the insect vector For the examination of the former a consideration of India where all the circumstances have been worked out most carefully will suffice but it may be assumed that the same factors are applicable in other countries also The insect vector appears to be in India at least the sand fly *Phlebotomus argentipes*, as to the role of which we shall revert under transmission This sand fly happens to prevail in India at least under the same circumstances and in the same places as human kala azar and only to a very slight extent outside them In fact it was this agreement in distribution that led Napier, Knowles and other officers[49] working in the Calcutta Research Laboratories to concentrate on its possible role as a vector This is mentioned by L Everard Napier[48] in his book The Principles and Practice of Tropical Medicine (1946) as follows The workers in the Calcutta School of Medicine were impressed by the fact that of all the various blood sucking insects under suspicion the local distribution of the sand fly *Phlebotomus argentipes*, corresponded most closely with the distribution of kala azar

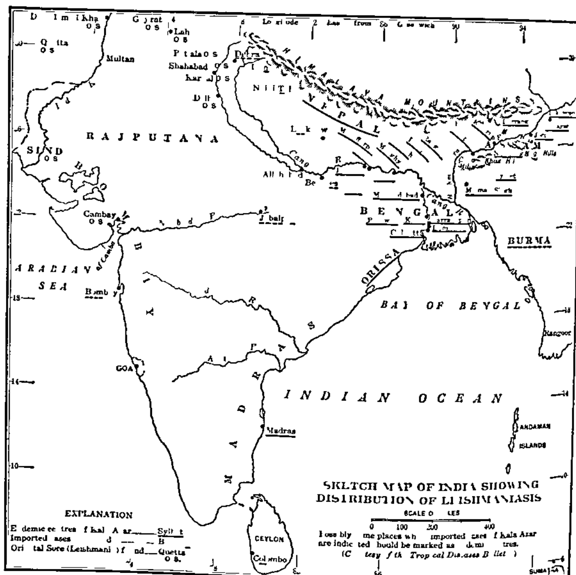


Fig. 4.

Fig. 4 Sketch map showing distribution of leishmaniasis in India

F1 6—Map of Mediterranean Region Showing Distribution of Kala Azar and Oriental Sore
(C i sy f th T p l D B ll t)

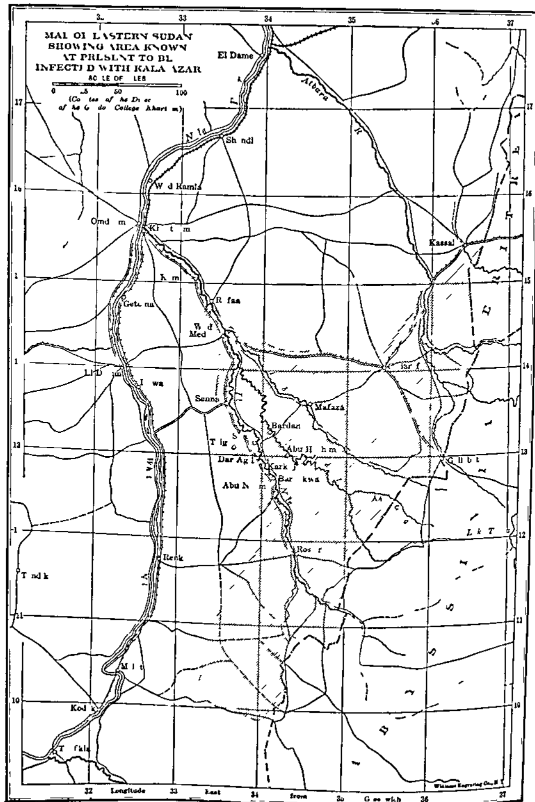


Fig 5 Sketch map showing distribution of leishmaniasis in Eastern Sudan

Other sand flies capable of spreading the local Leishmaniasis, are present as well in other countries It seems that Nature designates the vector to pick up by its suctorial apparatus, develop and transmit the disease according to its character and wherever it prevails Thus *P argentipes*, the vector in India would seem to be replaced by *P major, var Chinensis in China P longicroni or perhaps some others in the Sudan P perniciosus* in the Mediterranean and so on Where the appropriate sand fly prevails and man leads the life of the poorer classes as for instance in India or the type of existence common in the villages and little towns of Southern Italy kala azar is able to prevail also Why it should assume epidemic virulence at certain times and revert to the slower and more endemic character at others is a difficult question to answer although probably connected with the killing off of the non immunes of a generation with a pause for the production of another

In all such areas the factors which appear important are (a) close human contact, (b) house infection (c) association with large water courses the Ganges the Blue Nile the Rahad and (d) the prevalence of compounds in which much vegetation and much association with hens rabbits ducks etc is the rule Rogers noted how the transferance of the inhabitants from their infected houses to new habitations even so near as 300 or 400 yards away was enough to cut out the infection and yet the site of the old building was often fatal to others even if the *house had been burned Sand flies continue to live in the cracks and* holes of the old floors and do not follow a family for more than the distance of their flight a very short one But woe to the new comers who attempt to build their shanty in the same spot as that left by the former owners The growth of trees around the houses the presence of poultry dogs and cattle the puddled floors and defective sanitation all these so favorable to sand flies, appear to count in the prevalence of the disease

Kala azar ceases to be prevalent at elevations over 2 000 feet and the average temperature must be neither very cold nor very hot The climate must be moist The time of the Monsoon presents a very favorable one for the infection that is the time of the greatest prevalence of the sand fly the *P argentipes* in India Age and sex do not appear to *have much influence on the problem in India but the infantile type* seems to be of some importance in the Mediterranean area although there seems to be more adult kala azar there than was realized at first

Infancy says Debono[7] is not to be regarded in its strict sense of the

first year of life In Malta the age distribution of the last 200 cases was as follows

0-1 year	10	4-5 years	20
1-2	76	5-6	8
2-3	55	6-7 "	2
3-4	26	7-8 "	3

In the Mediterranean states Shortt in the discussion which followed 10 to 11 per cent of cases are in children at the breast', whereas in India the percentage of cases in children under 1 year old is 0 06 per cent'

Rogers as the result of close enquiry is of opinion that the disease usually is contracted during the cold season in India where the areas affected have unusually mild weather He associates these facts with his original observation that a moderately low temperature presents the optimum conditions for culture of the parasite to its flagellate stage and suggests that a prolonged and mild cold season may lead to increase of cases by affording the best conditions for infectivity of the insect host which he assumes to exist A study of sporadic cases shows that in India neither age nor sex has any preponderating importance, that no race is exempt if exposed to infection, and above all that within endemic areas the disease is practically confined to those persons who live under native conditions or in close contact with natives Of the cases arising among Europeans all had been for long periods in the country (3 had been over 20 years in India), belonged to the same class as those born in Calcutta and like them were living in parts of the city where their houses were surrounded by those of the native inhabitants and under conditions of overcrowding and bad sanitation

It is clear that we have to do with a disease which under ordinary conditions is spread only with difficulty and only to close associates The prolonged course of the malady makes up for its comparatively low infectivity by spreading out the period of potential danger over a long time and keeping the virus alive in its human host from one season to another Any climatic or other factor favorable to transmission will especially if operative over a longer period than usual multiply the foci of infection and tend to bring about a subepidemic instead of an endemic type

Mode of Transmission

The discovery by Rogers of a flagellate stage in cultures of *Leishmania* parasites the low temperature at which these cultural forms develop the fact that the parasites circulate in the peripheral blood and the general analogy with the closely allied trypanosome diseases strongly suggested to him that the disease was transmitted by an invertebrate host in all probability a blood sucking insect In India the work of Patton proved that development took place in the bed bug but as we have already stated this observation was practically proved to be of no importance in the spread of the disease In Italy Basile' went far towards showing that both canine and infantile kala azar were transmitted by fleas but his claim has at present been abandoned for the sand fly transmission

Against the insect vector theory it was argued that although almost always present the parasites were very few in the peripheral blood and usually insufficient to insure infection of blood sucking insects On this and other grounds several authorities argued in favour of infection by mouth

As long ago as 1905 Statham and Butler[16] suggested the possibility of a water insect as an intermediate host and a similar suggestion was made by Archibald[13] in 1914 the assumption being that the water insect or infective stage of leishmaniasis arising from it might be swallowed by human beings Nackie' found Leismann like bodies in the feces of kala azar patients and laid stress on contact as important in the spread of the disease in a restricted area under his close supervision Perry in 1922 found masses of Leishmania parasites in the ruptured intestinal villi of cases from India and Shortt in 19 3 reported the recovery of *Herpetomonas donovani* from the urine of a kala azar patient and was able to demonstrate them in the urine of more than one case The nasal mucus has also been found infected in a fair proportion of patients

The Sand Fly —In spite of all these probabilities however the finding of a flagellate stage and the development of this stage at a low temperature 2 C pointed so strongly towards an insect vector that research still was directed to the finding of some fly or some insect which might carry the parasite from one human host to another as in the case of malaria or filariasis Here was a definite fact to be considered Wenyon had found in the sand flies of Aleppo the leptomonad stages or something very like them of *Leishmania tropica* and

had published his observations upon them in 1911 Was there not in India some sand fly that would equally satisfy the conditions necessary for the transmission of *Leishmania donovani*?

The sand fly *Phlebotomus argentipes*, is rightly regarded as a denizen of every kala azar area in India To quote Napier, 1927, once more Recently Barraud has reported the finding of large numbers of *P argentipes* in the kala azar endemic areas of Madras town, the Kala Azar Commission has found large numbers in the endemic areas of Assam the writer and other workers at the Calcutta School of Tropical Medicine have found large numbers in the kala azar infected villages around Calcutta as well as in the City itself In other words, the members of the Calcutta School of Tropical Medicine, R Knowles L E Napier and R A O Smith[10] were quite in line with the direction of profitable research when they discovered herpetomonads, similar to those found by Rogers in cultures in the mid-gut of *P argentipes* in 43 of 102 flies fed on the blood of kala azar patients, at the same time finding not one of 46 flies fed on ordinary healthy persons to be infected Here then was a possible insect vector to be followed up with the greatest vigor At the same time as if to furnish a convenient laboratory animal for further experiments Young and Hertig[5] (1924) discovered that the striped hamster *Cricetulus griseus*, was susceptible to a chronic progressive and usually fatal disease on the intraperitoneal inoculation of *L donovani*—one animal has actually been found naturally infected—and could therefore be used instead of man for the sorts of research which would become necessary

Knowles Napier and Smith[10] as has been stated, called fresh attention to the sand fly and presented incriminating evidence that the *P argentipes* was involved Eleven batches of laboratory-bred female *P argentipes* were fed on unselected kala azar patients in hospital On dissection on the third and fifth days it was observed that 25 out of 56 flies had a herpetomonad infection of the mid gut Forty six flies bred under the same conditions were fed on the peripheral blood of persons not suffering from kala azar and in no case was a herpetomonad infection observed Napier in 1926 was able to conclude that Every viable parasite ingested caused a flagellate infection of the gut of the fly if the temperature conditions were suitable, that the monsoon was the most suitable period for development and that during the coldest months practically no development took place Meantime the Kala Azar Commission in 1926 showed that by keeping artificially bred speci

mens of *P argentipes* at the monsoon temperature 83 F a well conditioned fly could be produced which would feed readily a second third and fourth time They showed too, that in thinly sectioned specimens

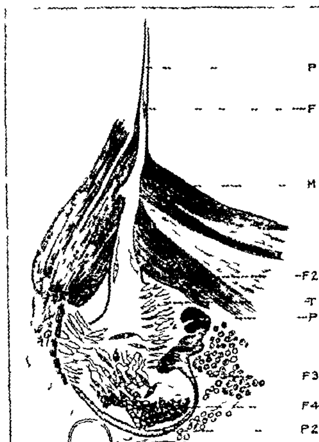


Fig 7 *Phlebotomus argentipes* showing pharyngeal infection with *Herpetomonas donovani* (after Shortt Barraud and Craighead Ind J of Med Research 192) P = Pharynx F = Flagellate near anterior end of pharynx F2 = Flagellates anterior to crinkly portion F3 = Flagellates breaking free from main mass of growth F4 = Massive growth of flagellates at posterior end of pharynx (By kind permission of Sir Leonard Rogers)

there was a massive infection of the pharynx and an infection of the buccal cavity extending distally to the salivary pump (Fig 7) Every visible form of the parasite taken up by the fly under suitable conditions of temperature and humidity developed into a flagellate rapid

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with O Theodor and G Witenberg[2] in Canea and other places in the transmission of *L infantum* by *P perniciosus* and *L tropica* by *P papatasi* Lastly while it is true that Adler and Theodor failed to infect a man with the entire mid gut of an infected sand fly in an experiment with *L infantum* it is also true that while this experiment always failed experiments with the bites of the infected sand flies often succeeded It seems that the herpetomonas has to undergo some development in the proboscis of the sand fly to become capable of infecting man

All of these facts have no doubt a meaning They may perhaps be connected with the varying degrees of immunity which have been mentioned or with the difficulty of infecting persons with cultures in some cases But take it all round it appears certain that the sand fly is a principal vector of kala azar notably in India The very similar conditions under which the flies and the humans live, The flies are found in cow sheds, human sleeping quarters and occasionally in certain other situations such as fowl houses the close association between the in sanitary but thoroughly native conditions which seem to be common to mankind and to *P argentipes* in the affected parts of India the fellowship of existence in such things as the presence of trees, puddled floors accommodation of the cattle so dear to the sand fly the presence of ducks dogs, chickens etc the restriction to certain temperatures, under 100 F and over 50 F the similar timing of human cases and of sand flies to the monsoon period and the identity of the appropriate elevation not over 000 feet all these circumstances concur to make out a good case for the sand fly as a vector if taken along with other evidence of a distinctively experimental nature

Finally there is the recent observation of Swaminath Shortt and Anderson (194) who transmitted the disease to out of 6 human volunteers by feeding infected *P argentipes* upon them these 6 persons being born in and living throughout the experiment in districts outside the endemic areas This definite finding appears to the writer to place the transmission of infection by *P argentipes* to man in India beyond doubt

In other geographical areas however apparently there are other vectors Thus in the Sudan Kirk and Lewis (1941)[5] have provided good evidence in favor of *P langeroni var orientalis* In China *P major, var Chinensis* has been implicated by Young and Hertig (1926) In Italy and the Mediterranean basin Adler and Theodor (1931) have shown that *P perniciosus* is to be held responsible

multiplication took place in the gut of the fly, and infection passed forward so that, if the fly took a second meal, until the seventh day the buccal cavity actually became infected, and that, if this fly fed a third time it was practically impossible for contamination of the wound not to occur' (Fig 7)

This and the 'blocking" of the fly by intense multiplication of the flagellates which produces a condition in the mid gut of the insect very much akin to that of blocked flea" in plague, seems to indicate the importance of the sand fly and in fact, the *Phlebotomus argentipes* is now accepted as the principal vector, perhaps the only vector, for the Leishmania of visceral kala azar in India Other phlebotomi are incriminated as the vectors elsewhere

At the same time there are certain reasons for hesitating to accept the sand fly as *the only* means of spread, at least some urge the importance of other methods Strong [4] for instance, in the seventh edition of Stitt's Diagnosis Prevention and Treatment of Tropical Diseases' (1944), speaks of the frequent failure to transmit to human beings infection through the bites of infected sand flies and points out that human susceptibility to inoculation appears to be very slight" He quotes some of those who have failed or who have succeeded by direct methods only Maggiore [5], in 1925 inoculated infants with bone marrow and cultures of *L infantum* but obtained negative results He also failed to infect babies by the inoculation of *L tropica* from cases of Oriental Sore On the other hand he quotes Adler and Theodor [6] who in Jerusalem, succeeded in infecting adults with the parasite of Oriental Sore by direct inoculation from human beings He mentions the failure of Adler and Theodor [6] to infect an adult by the inoculation of the entire mid gut of two sand flies, *P perniciosus*, which had become heavily infected with *L infantum* after feeding on an infected Chinese hamster He quotes also the failure of Da Cunha Marques and Chagas[7] to infect two human beings by the inoculation of 4 c c of a rich culture of *L chagasi*, as the South American parasite of leishmania is now called Admitting all this, however, it is necessary to recall that there are certain factors to be remembered which tend to minimize the importance of each of these findings The failures of Maggiore [5] and of Da Cunha Marques and Chagas must be admitted but neither of these authors would now hold their negative experiments to be final Adler's success in direct inoculation from an infective sore to healthy persons is a thing to be noted, but it hardly counts against his subsequent work,

determining factor in the spread of the disease They say in short that the sand flies feed on the unbroken skin of dogs and then transmit the disease to humans by biting them and introducing the parasites

PATHOLOGY

The organs chiefly affected are the spleen the liver the bone marrow the lymph nodes and the intestine but the parasites have the power



Fig 9 Section of liver from a case of kala azar note endothelial cells containing many parasites

of invading many tissues and lesions may be found in the testicles the thymus the suprarenals and as has been indicated often in the skin

The *spleen* is as a rule greatly enlarged In the acute stages the enlargement puts a considerable strain on the capsule so that rupture has been known to occur In later stages the capsule thickens so that this accident is unlikely to happen The organ although so much enlarged retains its shape but its internal structure is profoundly altered as described later A spleen measured by the writer was 33 cm by 16 cm and the weights of two spleens in the Royal Army Medical Corps Col

While one must accept the fact that monkeys have been infected by swallowing non-flagellate parasites and that this method, therefore is likely to infect human beings, especially perhaps in epidemic periods, when the infection from numerous cases is available for non resistant persons still it has now been proved that the sucking of blood from cases by sand flies and the biting in turn, of the healthy by these insects is able to cause kala azar in the latter The presence of parasites in the

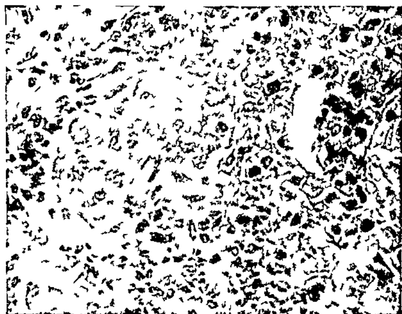


Fig 8 Section of liver from a case of kala azar

blood of infected people even though in very small numbers appears to be almost invariable and that strange complication, post kala azar dermal Leishmaniasis to be described later in this chapter is known to be present and be infective for sand flies in recovered cases often for years after the illness of these infected persons a finding which makes the role of the sand fly all the easier, even if the parasite is very rare in the blood

Adler, Theodor and Witenberg[50], in fact, find that the unbroken and apparently healthy skin of dogs infected with kala azar is more often infected than the ulcerated portions This they say confirms the view brought forward in previous papers that the cutaneous ulcers are not of epidemiological importance and that the unbroken skin is the

row of the long bones being red in color and often diffluent The *lymph nodes* especially the mesenteric nodes often are enlarged livid in color and in some cases almost diffluent on section Although often found al most normal in appearance Perry and also Christophers have found marked ulceration Perry in the *jejunum* and Christophers in the *large intestine* The columnar epithelium says Perry covering the villi had disappeared and the basement membrane furnished a delicate limiting sheet for each little swelling The internal structure of the villi was com pletely altered owing to an intense proliferation of the cells lining the lymph channels In the great number of villi the basement mem brane was intact but in many instances it had ruptured from over distension and liberated the enclosed endothelial cells The parasites were present in larger numbers in the same intracellular situation in the base of the villi (Figs 10 and 11) In the centre of the villi they had undergone rapid multiplication and they were present in enormous numbers in the endothelial cells distending the extremities of these struc tures In many of the villi large numbers of endothelial cells had broken down and the parasites were lying mixed with the debris of necrotic cells free in the villus

Morbid Histology

In the spleen the liver the bone marrow and the intestines in all the organs in fact which are infected the essential changes observed are the same The normal tissue structure is penetrated as it were by masses of large mononuclear cells of reticuloendothelial origin, which contain the *Leishman dono in* bodies often in enormous numbers (Figs 1 2 and 9) In the opinion of most observers these cells are pro duced by the invasion of the reticuloendothelial elements of the blood and lymph capillaries by the parasites and the subsequent enlargement and alteration of these elements to form the masses of large mononuclear cells referred to The change is not universal in the organs areas of more or less normal tissue alternating with zones of intensely infected cells the latter being as a rule easily recognized with a moderate mag nification The general impression is that areas of granulation tissue seen with higher powers of magnification are to be observed distended with parasites, which are almost entirely intracellular although in smears from organs they tend to lie free or in masses held together by what is probably the cytoplasm of ruptured cells There is not usually much

lege Museum are recorded as 48 and 87 ounces (1,500 and 3 000 grams) respectively The enlargement of the *liver* usually is less than that of the spleen The tendency to cirrhotic change (Fig 8) is important as it brings about loss of function and mechanical disabilities, such as ascites, which add greatly to the discomfort and, indeed, danger of the patient The Kupfer cells are said to be often greatly enlarged and to be

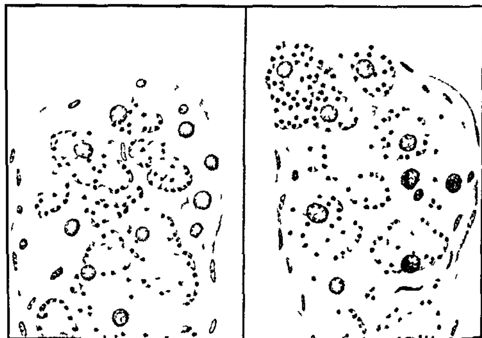


Fig 10 Section of intestinal villus showing intracellular and free *Leishmania* parasites basement membrane still is intact semi diagrammatic

Fig 11 Section of intestinal villus showing ruptured basement membrane and escaping free parasites and endothelial cells filled with parasites semi diagrammatic (Figs 10 and 11 from paper by Brevet Lieutenant Colonel H Marrian Perry R.A.M.C in Jour Royal Army Medical Corps)

laden with parasites (Fig 9) a phenomenon which is very much in keeping with the reticuloendothelial nature of the disease Adler Theodor and Witenburg for instance say about a dog which they dissected that the liver showed intense proliferation of Kupfer cells not only within the capillaries but also among the parenchyma cells outside the capillaries

The *bone marrow* is invariably the seat of marked changes, the mar

row, the red corpuscles and the polymorphonuclear leucocytes In a series of cases tabulated by Rogers while 30 per cent had counts of four *million and upwards* , *per cent had between two and a half and four* million and over 15 per cent less than two and a half million red cells per cubic millimeter The color percentage falls in proportion to the diminution of red cells the color index remaining about normal It will be noticed that the type of anemia is not that of chlorosis an important point in the differential diagnosis between this disease and ankylostomiasis It tends rather towards that of pernicious anemia normoblasts being often seen and a tendency to basophilia and to some degree of poikilocytosis being present

The polymorphonuclear leucocytes are of all the leucocytes the most affected They are reduced in number because not only is production diminished through changes in the marrow but the using up of phagocytes in coping with the infection is very great The production of the mononuclear leucocytes is less interfered with the lymph nodes being as a rule less although considerably affected as compared with the bone marrow but here too there is diminution in output and increased demand The net result is that a total leucocyte count shows in practically every case a marked leucopenia This condition may be extreme In a case under the care of the writer the total leucocyte count was on one occasion 870 per cubic millimeter The leucocytes are almost always diminished to an extent far greater than the red corpuscles and the ratio between these elements is an important diagnostic feature In over 50 per cent of a series of cases Rogers found the ratio of leucocytes to red cells to be from 1 to 000 to 1 to 4 000 or below this A differential count shows a relative increase of mononuclear elements this affecting especially the large mononuclears which tend to be up to or over 15 per cent while the polymorphononuclears fall very low Napier gives the contrast between a typical Indian with kala azar of about , months standing with a normal Indian as follows

	Kala Azar Case	Normal for an Indian
Haemoglobin	60%	65 9%
R B C	3 000 000	5 000 000
W B C	500	6 000
Polymorphonuclears	30% or 750	70% or 4200
Small Lymphocytes	51 % or 1 75	8% or 1380
Large mononuclears	16% or 450	5% or 300
Eosinophiles	1% or 25	-% or 120

inflammatory reaction in the invaded organs, but collections of leucocytes sometimes are seen around the areas of infected endothelial cells and fibrotic changes may arise in chronic cases, an intralobular type of cirrhosis being common in the liver Areas of granulation tissue containing many parasites are found sometimes in the walls of the small and large intestine and may lead to extensive ulceration and it is said, even to perforation but in the writer s opinion these must occur very rarely

Although the reticuloendothelial cells are so markedly invaded and altered the parasites very seldom enter, although they may replace, the functional cells of the liver and spleen The loss of efficient cells in all the affected tissues is however profound owing to the pressure injury and displacement of the functional cells by reticuloendothelial elements, to interference with blood supply resulting from changes in the capillary walls and to the mechanical conditions following the slow reactional changes around the affected areas It is these changes rather than any toxic action of the parasites that produce the symptoms of the disease The presence of a toxin causing the pyrexia, wasting, anemia and other symptoms of the disease often has been assumed, but this has never been proved and the theory appears quite unnecessary The injection of enormous quantities of highly infected spleen juice or bone marrow has no immediate effect on laboratory animals, and the inoculation of great volumes of cultures leads to no toxic symptoms The following quotation from Laveran probably expresses the real facts of the case Il est probable que les Leishmania du kala azar agissent en se multipliant et en detruisant les tissues parasites cellule a cellule, et non par l effet d une toxine Les produits de desintegration, en penetrant dans le sang produisant la fievre et l alteration des cellules du fois de la rate et de la moelle osseuse entrainent la mort"

The Blood

Cellular Elements—In view of the fact that the marrow is one of the tissues most heavily invaded by the parasites and that their activity leads to the formation of masses of enlarged and infected reticuloendothelial cells and to a corresponding depreciation of the function of the marrow, it is to be expected that there will be interference with the production of the cellular elements of the blood As a matter of fact cases present a marked diminution of the cells originating in the mar

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	Kala Azar Case	Normal for an Indian
Haemoglobin	60%	85 9%
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W B C	2 500	6 000
Polymorphonuclears	30% or 750	70% or 4 00
Small Lymphocytes	51% or 1 75	8% or 1380
Large mononuclears	18 or 450	5% or 300
Eosinophiles	1% or 25	% or 120

Cases of agranulocytosis, sometimes fatal, have been reported in advanced instances of kala azar.

Platelets often are decreased to cause sometimes defective clot retraction.

[*Blood Chemistry*.—Serum globulin usually is increased, as a rule being in excess of 2.5 gm. per 100 c.c., while serum albumin is decreased to 4.0 or 3.5 gm. per 100 c.c. or even less. In an occasional case the hyperglobulinemia more than compensates for hypoalbuminemia with a resultant hyperproteinemia. After treatment these figures gradually revert to normal. The increase in globulin is chiefly in the euglobulin fraction, a gamma globulin by electrophoretic analysis. A cold precipitable protein has been described in the serum which redissolves on return to room temperature. The globulin in leishmaniasis patients binds a subnormal amount of calcium.[9] Total serum calcium usually is normal or slightly subnormal.—Editor.]

SYMPTOMATOLOGY

The clinical picture of the advanced case of kala azar is very characteristic. The marked wasting of the extremities, the tumid abdomen, the characteristic pigmentation of the skin, the anemia and the general weakness, lassitude and depression are striking in the extreme.

The disease assumes two main types, the one rapid and fulminating, the other much slower and more chronic, but both tending, if untreated, to the same fatal termination. The former runs its course, as a rule, in three fairly definite stages.

First Stage.—After an incubation period of indeterminate length, the minimum on record being about 14 days or less according to Muir and the maximum up to 6 months or more to judge by some of the cases reported since the late war, the first stage may open with an attack of an acute febrile illness, often mistaken for typhoid fever, during which the spleen enlarges, and the temperature runs an irregular course; the differentiation should not be difficult, however, as there is always the leucopenia to guide us in place of the absence of any marked diminution in the leucocytes in typhoid. Manson Bahr,[6] for instance, gives the leucocytes in kala azar as follows: Below 3000 in 95% of cases
2000 in 73% of cases
1000 in 42% of cases

In the fever charts of kala azar (Fig. 14) there is one type which reminds us of typhoid fever, but the others may be sufficiently character

Fig 1 Patient with kala azar note emaciation and outline of enlarged spleen (by kind permission of Sir Leonard Rogers)

Fig 13 Patient with kala azar note emaciation and enlarged abdomen lower edge of spleen is outlined (by kind permission of Sir Leonard Rogers)

istic This first stage tends to be followed by an apyrexial period during which the patient seems to be improving, but the amelioration does not last long

Second Stage—In this stage the anemia becomes more and more pronounced, and all the symptoms gradually increase The spleen and usually the liver continue to enlarge and to become hard, the patient loses flesh and strength, and the temperature pursues an irregular course uncontrolled by quinine or any of the usual antipyretic remedies

Third Stage—In the untreated case the patient passes by slow degrees into the final phase in which the clinical picture is merely an exaggeration of that just described The wasting becomes so extreme that the body, except for the abdomen, is almost a skeleton (Figs 12 and 13) The extremities and sometimes the face may be edematous, the superficial veins of the abdomen often are engorged and the spleen, which may be actually visible through the wasted abdominal wall, reaches to the right of the umbilicus and downward into the iliac fossa There is often considerable ascites due to cirrhotic changes in the liver The pigmentation of the skin may become very marked, and there are cutaneous ulcers in which the parasite is sometimes to be demonstrated Diarrhea of a dysenteric type is common at this last stage, and the case terminates, as a rule, from some intercurrent condition, usually bacterial such as cancrum oris or septic pneumonia From statistics collected by Mackie[1] it would seem that about 65 per cent of untreated cases terminate in a year or less but the disease may be much longer, and about 10 per cent. continue for 1 or 2 years

The Types of Fever—The main characteristic of the pyrexia in kala azar is its irregularity (Fig 14) Periods of low, remittent and intermittent temperature alternate with waves of high fever, and there often are considerable intervals during which the temperature deviates but little from the normal A point, to which attention was first called by Rogers[2], and which is regarded as more or less characteristic of kala azar, is the 'double rise in each period of 24 hours This is not constant throughout the whole course of the disease, but it is nearly always noted at some period and usually during waves of high temperature. There may be not two but several 'spikes' a day, and the feature appears to be simply an expression of the irregular pyrexia already noted

Much work has been done on the question of types of pyrexia in kala azar by Sir Leonard Rogers[60], whose records include complete four hour charts of all the cases treated in the European Calcutta Hos

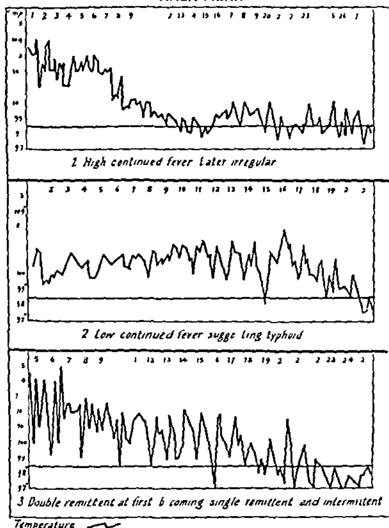


Fig 14 Fever charts illu trating the three commonest forms of fever in kala azar (by kind permission of Sir Le nard Rogers)

pital for some 20 years He considers that a study of the temperature is of great importance, especially in the recognition of early cases of the disease from the enteric group A high remittent type of fever is common in the latter group but rare although not unknown, in kala azar The double rise is regarded by him as practically diagnostic of kala azar and this feature even in a high remittent chart is to be viewed with grave suspicion that the condition is kala azar A low continued type of temperature with diurnal variation not exceeding 2 degrees but without a drop to normal is often met with All students of this disease should read the description of types of fever in kala azar given in his book Types of Fever in the Tropics [60] We reproduce here (Fig 14) three varieties of temperature chart as given by him in his work, with Megaw, on Tropical Medicine' [4], which are well worthy of careful study

The main feature of the disease is perhaps, the intense asthenia The patient is reluctant to undergo any exertion and resents the fatigue and disturbance of examination This asthenia is especially noticeable in children There is no attempt to play no interest in things or people The infant wrinkled and wasted has an appearance of premature old age and world weariness and only desires to be let alone In the early stages there may be considerable pain in the splenic region associated with the increase in size of that organ. A curious feature often noted is abnormal appetite In a patient under the care of the writer this feature was pronounced and the craving for food was very distressing Night-sweating often is noticed and may be very marked No characteristic changes occur in the respiratory system except such secondary changes as have been mentioned A scorbutic and ulcerative condition of the gums is present often Dysenteric diarrhea is frequent in the late stages and irregular diarrheal attacks are not uncommon during the course of the disease

The kidneys are but seldom affected by the parasite, and the urine generally is normal but a slow interstitial nephritis may occur A recent finding is that about 7 per cent of cases pass the parasites of kala azar in their urine The Leishman Donovan body has been found to infect the testicles in a fair number of cases

The blood condition and the alteration of the endothelium of the capillaries has been described already Attention has been called by some writers to a tendency to fragility of the walls of the peripheral capillaries, a child for instance developing numerous petechial hem

orrhages while being examined by a doctor This may have been due in part to the lowered coagulability which is common to the disease

The disease is however usually brought to an end by treatment now a days and it is unusual to meet with these disturbing symptoms This tendency to recovery is however sometimes interrupted by the discovery that although cured of the visceral disease the patient has



Fig 15 Post kala azar dermal leishmaniasis h wi cutaneous macul r erup tion on face infected with kala azar parasites (by kind permission of Sir Leonard Rogers)

run on into the curious state of *post kala azar cutaneous leishmaniasis* (Fig 15) a condition which occurs in at least 5 per cent of all cured cases The patient of 3 or 4 years of age who has been in the best of health during the interval now complains of skin trouble This condition first described by Brahmachari[6] and closely studied by Napier and Das Gupta is described by Rogers as follows The most typical condition is the appearance of nodules on the skin (Through the kindness of Sir Leonard Rogers it has been possible to reproduce here his figure of post kala azar dermal leishmaniasis (Fig 15) in which numerous *L donovani* parasites can be found) Leishmania containing no

dules have been found often in the tongue. Depigmented areas and erythematous or butterfly rashes are common also together with the less frequent verrucose, papillomatous and exanthematous types. L. E. Napier has demonstrated the same organism in the skin of many cases without evident lesions and he has infected sand flies by feeding on such patients who may thus prove to be a source of infection very difficult to detect.

DIAGNOSIS

In the early stages the disease may be confounded easily with typhoid fever to which the similarity is very close, although careful examination of the blood may provide the clue as already described. At all stages of the disease it is liable to be mistaken for malaria which may actually coexist with it and cases may present a striking resemblance to malta fever. The resemblance to severe ankylostomiasis may be very great but the type of anaemia is different and this point together with the type of pyrexia should prevent mistakes from arising. Patients suffering from the more chronic type have to be investigated very carefully to exclude other splenomegalies notably Banti's disease in which the leucopenia and lowered blood coagulability add to the resemblance.

The clinical picture, the characteristic blood condition, the type of pyrexia and the locality of origin will all help, as will also the negative findings for other diseases such as the absence of the Widal reaction, failure of blood, stool and urine culture to afford evidence of the enterics and the inefficiency of quinine and quinacrine hydrochloride (atabrin) treatment as compared with their efficiency in malaria. Serological methods have been tried, and the writer can bear personal testimony of how successful Noguchi was in differentiating *L. donovani* cultures from *L. tropica* by means of his agglutination and absorption tests. These tests can, however, be ignored, if the parasite is found.

Examination of the Peripheral Blood for Parasites.—(a) As the parasites are often found in the leucocytes Wright's method of spreading films on a slide employed by him in the opsonic index, should be used so that the parasites, if any are present, may be quickly searched for at the end of the slide where often they may be found.

(b) A small quantity of blood, about 0.5 c.c., should be citrated and allowed to settle, films being carefully made from the layer of leucocytes that forms upon the deposited red corpuscles.

(c) The remains of the blood should be used on the NNN medium,

which has been described already for cultures and with a fair prospect of success In all cases films should be searched through for parasites before the peripheral blood is admitted to be free from parasites

Spleen Puncture—Attended with a slight degree of risk, this method although perhaps the surest of any should be deferred until all the others have failed Microscopically as Napier says "there is an filtration of the spleen by masses of heavily parasited macrophages these encroach on the lymphatic follicles (Malpighian corpuscles) which eventually disappear almost completely There is considerable enlargement of the vascular spaces The large parasited macrophages appear to dominate the whole picture" It can be imagined that such a spleen although well calculated to give a positive on puncture might under occasional circumstances allow of some degree of bleeding

Liver Puncture—This is safer although less effective than spleen puncture and often leads to a positive diagnosis The end in view is to obtain in the needle a little of the liver substance rather than blood from a vein or capillary and the more blood withdrawn the less the chance of a positive result

Sternal Puncture—This procedure intended to make possible the examination of a film from the cancellous bone marrow of the sternum is easily done and very effective A film from the cancellous matter from the head of the tibia may be similarly obtained if preferred Any needle appropriate for sternal puncture should be used

Puncture of a Lymph Node—Although not so well reported on from India this method has given valuable results in the Mediterranean basin in China and in the Sudan The skin over the lymph node is rendered sterile the node is steadied by pressure between the thumb and forefinger and the needle then is inserted and a small portion withdrawn under pressure and used for making slides and for culture

From all these methods spleen liver lymph node and sternal puncture in addition to the making of films cultures should be made in NNN medium These sometimes prove positive even when the films have been negative

It is to be noted that now with the much increased hope of successful treatment spleen puncture should be attempted always if all the other methods have given negative results The degree of risk is very slight, and a positive result must be obtained whenever possible

Various chemical tests have been devised for kala azar which are in the hands of experts extremely useful

The Aldehyde (Napier) Test—This is a rather late reaction, the test not being fully developed for about 4 or 5 months It takes about 4 months to disappear after cure It proved to be correct in about 70 per cent of cases that reach the Out Patient Department of an Indian hospital

To 1 c c of clear serum are added one or two drops of commercial formalin In a strongly positive result the serum becomes solid and opaque within a few minutes If it becomes completely opaque within 4 hours, the result is still considered positive In a negative the serum remains crystal clear, although it may solidify"

The Antimony (Chopra) Test—The serum is diluted 10 times with double-distilled water and is placed in a narrow-bored tube To this is added a 4 per cent urea-stibamide solution by means of a Wright's pipette the tube being rotated between the palms to mix the contents In a strongly positive reaction there is a heavy flocculent precipitate This passes through various degrees of positive to a mixture of the two fluids without any precipitation

Prognosis

In untreated cases the prognosis is grave in the extreme and in the Assam epidemic the mortality is said to have been about 96 per cent Still cases even untreated do recover spontaneously, and one or two patients definitely diagnosed by the demonstration of parasites by Bousfield[11] in the Sudan in 1908 09, were found to be quite clear of the disease by Thompson and Marshall _ years later The introduction of treatment with antimony tartrate and, later, still more so, with the pentavalent antimony compounds has changed completely the outlook for kala azar patients and provided a case comes under treatment before the disease has reached a very advanced stage, there is every prospect of a speedy cure Ever since Vianna and Machado[1] (1913) tried potassium antimonal tartrate for the treatment of the allied disease, espundia the whole direction of the search for methods of treatment in kala azar as been changed along a new course and the results have been striking in the extreme and promise to be even greater in the future

Before proceeding to the discussion of treatment, however it is as well to consider for a moment what the human body is able under certain conditions to accomplish for itself in the way of cure The experi

ments in serology and immunity already referred to show, as we think there there is a definite response in the direction of resistance to the parasite, although this may for all practical purposes be completely overcome in the advanced stages of the disease It should be remembered that after a certain stage of the illness recovery implies not only the killing off of the parasites but also the getting rid of the new cellular elements brought into being by the infection The spontaneous recoveries following cancrum oris and even the induced recoveries following the successful treatment of advanced cases show that the parasites once dealt with the body is capable of reconstituting its altered and injured organs Nothing is more striking than this power of getting back to health when the parasites have been killed even from stages of the disease that appeared to have passed beyond any hope of functional resurrection

Treatment

Of the many methods of treatment tried in the past the majority may be dismissed in a few words

Splenectomy advocated on grounds of analogy with other forms of splenomegaly is unlikely to succeed in a generalized disease like kala azar and has been found useless in practice Quinine in large doses at one time had its advocates notably Rogers [9] and was said by Dodds Price [5] to have reduced the mortality from over 90 per cent to 75 per cent in a series of 500 cases The author has seen definite improvement of some weeks duration to follow its use but the improvement which was not maintained was probably due to the successful handling of a complication Guided by the observation that bacterial complications sometimes lead to cure Rogers and others at one time tried treatment by inoculations with staphylococcus vaccine with a certain measure of success in a few cases but no striking results The use of killed *Leishmania* cultures as a vaccine has been tried too by several observers and Archibald has recorded the case of a recovery as the result but one case proves nothing as occasional spontaneous recoveries have been recorded

None of these methods has been found of any real value and the improvements noted can be matched by comparison with the temporary ameliorations tending to occur in untreated cases

Antimony Treatment

It was not until Vianna,[4] working in Brazil, tried the intravenous injection of antimony tartrate in the treatment of the mucocutaneous Leishmania disease known as espundia and obtained some conspicuous successes by this means that an effective treatment became at last available for kala azar. Numerous workers in fact simultaneously perceived the bearing of the results obtained by Vianna on the treatment of other Leishmania diseases. Di Christina and Caronia in Sicily, Castellani in Ceylon, Sir L. Rogers in India all proceeded to treat kala azar with tartar emetic given intravenously and all with very satisfactory results. Di Christina and Caronia were the first to publish in February 1915 a successful series of cases in which out of 8 children suffering from infantile kala azar, 5 were cured, 2 greatly improved and only 1 died and that one of nephritis. Rogers and Hume, working with European patients in Calcutta in whom the subsequent history could be followed, recorded a series of 35 cases treated on the new lines with 29 cured, 5 improved and only 1 death that due to phthisis but who, as shown by splenic puncture, had actually recovered from the kala azar. This method and subsequent modifications, and improvements have now placed the treatment on an assured foundation.

Antimony Tartrate.—This method as previously stated, is not free from danger and the following rules for its administration, formulated by Rogers should be observed. A freshly prepared solution of antimony tartrate in distilled water should be used of a strength of 2 per cent. Of this solution 3 or 4 c c or about one centigram of tartrate for every ten pounds (- kilos) of body weight should be the initial dose for an adult. The injection is made very slowly to allow dilution of the drug in the circulation of the patient, and the greatest care must be taken to avoid injecting the solution into the tissues as this causes great pain and inflammation. The dose is gradually increased but is never taken beyond 10 c c or 20 centigrams of the drug, a limit of - centigrams for every 10 pounds (- kilos) of body weight being rigidly adhered to. In debilitated children a 1 per cent solution is used, and not more than 1 c c of this or 1 centigram of the drug, is given at first, this being increased by 0 5 c c at a time up to a maximum of 3 c c. Coughing usually occurs just after or during the injection but may be ignored. Nausea and sickness indicate that the dose should be reduced. The patient usually experiences a metallic taste in the mouth almost at once after

the injection is commenced A temperature reaction usually follows Antimony tartrate however is now seldom used as better results and the giving of a larger dose of antimony follow the use of more modern preparations

The Pentavalent Antimony Compounds—We may state that the earlier treatment by tartar emetic, while it greatly reduced the mortality, especially in India and, although to a less marked extent in the Sudan, required a very cautious exhibition and the continuance over a very long period to ensure that sufficient antimony had been given before a cure could be expected

With the preparation of the pentavalent antimony compounds the earliest being introduced by Professor Hans Schmidt the whole situation changed Caronia[62] was the first to use *sodium para acetyl-amino-phenyl stibinate* in Italy in 1916, obtaining a promise of success In India *meta chlor para acetyl-amino phenyl stibinate* and *diethyl-amino-para amino phenyl stibinate*, the latter known as *neostibosan*, have been tried and reported on very favorably (19 3) by Napier and others [3] In adults these preparations are given intramuscularly by steppage" doses on alternate days as 0 1 gm 0 2 gm 0 3 gm the total varying from 3 to 10 grams dissolved in from . to 6 c c of distilled water Coughing vomiting and retching may result from overdosage but these complications very seldom occur

In Italy in infantile kala azar intramuscular injection of 0 1 gm and intravenous injections have been tried and well reported on In 19 2 Brahmachari[61] produced urea stibamine a very useful preparation In 1939 Adams and York were successful in the treatment of a case in England by means of *4 4/ diamidine stilbene* Adler and Rachmilewitz tried it in Palestine in cases of infantile kala azar Kirk and Sati[64] (1940) in eight cases in Sudanese and Napier and Sen[65] (1940) in India This drug was very successful, especially in 100 cases treated with it by Napier in India, but it is reported to give occasional toxic manifestations in the Sudan The advantage of the pentavalent compounds" says Napier is that they are very much less toxic and can therefore be given in much larger doses" In a series of more than 500 cases treated by him with neostibosan the mortality was only about 2 per cent

At the Wellcome Research Laboratory under the supervision of Wenyon much experimental work in the development of these chemotherapeutic remedies is in hand The writer has had the privilege of seeing T G Goodwin carrying out his remarkable experiments with

anti-kala azar remedies in these laboratories He inoculates hamsters intraperitoneally with kala azar parasites, proves them, after a time, to be suffering from the disease by removal of the tip of the spleen at biopsy, the portion of the organ removed being used to make impressions which, being stained, usually show the parasites in large numbers, and thus arrives at the effect of his "remedy" as a dose to a known infected animal which is treated only after it has been shown to be infected This method should greatly help to define the differences between the new preparations now being devised for the treatment of kala azar

CANINE KALA AZAR

The canine type of Leishmania, first described by Nicolle and Comte[9] in 1908 and thought by them to be identical with, and a cause of spread of, infantile kala azar has been a subject for much debate since its discovery and still presents difficulties from the epidemiological point of view The question of whether it can really be a source of human kala azar has been much examined in India, and it has been found only very seldom in dogs in that country, although so very common in man This has led many to regard the dog as an unlikely host for the widespread human disease On the other hand much evidence has been produced as to the presence of infected dogs wherever infantile kala azar of the Mediterranean type is common, and they have been found in the Sudan also as well as in Turkestan and many other places known to produce the infantile as well as the adult variety

Adler Theodor and Witenberg[9] very reliable observers, state definitely their belief in the spread of infantile kala azar from infected dogs to man in their observations on this disease in Crete "The findings in Canea" they report indicate very clearly the role of house dogs in the maintenance of the human disease The greater part of the cases found in 1934 could only have been caused by sand flies which had infected themselves on house dogs And again, in their conclusions, they say 'Human visceral leishmaniasis, canine visceral leishmaniasis and the sand fly *Phlebotomus major* have an identical distribution in Canea"

It seems to the writer that evidence such as this and the many points already brought forward by the discoverer Ch Nicolle, in favor of transmission of the canine disease to infants must be given their due

weight and the disease of dogs accepted as often a cause of the infection of children and others with kala azar Why the disease is so wide spread in India without any degree of dog infection being present remains a mystery and serves, perhaps, to indicate still another difference between the Indian kala azar and that of the Mediterranean and other places This disease remains in many ways still a subject for the closest research

LOCALIZED LEISHMANIA DISEASES

ORIENTAL SORE

Historical Introduction

Throughout Northern Africa throughout India and the nearer and further East at many points of trading military or colonial contact between Europeans and natives ulcers and sores of a peculiarly chronic kind had long been known and had been attributed in each place to some local influence or contagion It was natural that these sores should come to be called after the places in which they occurred, and many such names have become widely known throughout the East Such were the famous Delhi boil Bagdad boil, Allepo boil, Clou de Biskra, Clou de Gafsa and many others

Cunningham [9] had seen and described bodies" in Delhi boil in 1884 and there seems little doubt that what he observed were the parasites now known as the cause of the disease Riehl [0] in 1886 gave a good description of bodies in a case of Allepo boil but considered them to be encapsuled cocci Firth[31] in 1891 also noted the bodies and recognized their protozoal nature giving them the name of *Sporozoa furunculosa* But it was not until 1903 when James Homer Wright[14] of Boston examining material from a little girl born in Armenia and under treatment in the Massachusetts General Hospital found and clearly described the parasites of oriental sore which he christened *Helicosoma tropicum*, and called general attention to their protozoal nature, that the relation to each other of all these boils sores and boutons came to be discovered and their identity proved by the demonstrations of a common etiological cause According to Struthers in Cecil s Textbook of Medicine 7th

edition, page 452, W B Saunders Co, Philadelphia, 1947[73], "Borovsky, a military surgeon stationed at Tashkent, in 1898 described the parasite of oriental sore, recognizing it as a protozoon He also gave an accurate description of the disease As this account was in Russian, it was not known to Wright in 1903 when he gave an accurate description of the parasite now called *Leishmania tropica*" Wright's observation was confirmed speedily by James[3] in India, by Nicolle and Cathoire[33] in Tunis and by workers in many parts of the world

The close similarity of the parasite to that of kala azar was soon apparent, and the intimate relationship of these two protozoa was made still more evident when in 1908 Nicolle and Sicre[66] showed that the parasite of oriental sore, like that of kala azar, was capable of developing up to a flagellate stage in NNN medium Sergent, Parrot, Donatien and Beguet[67] in 1921 collected *P papatassi* in Biskra, an endemic centre for *L tropica*, and sent them to the Pasteur Institute at Algiers, a three days' journey These were emulsified in saline and inoculated into the skin of a man by scarification This man, later, developed a sore at the point of inoculation from which the parasites were recovered Much work has been done since then on the geographical distribution, the experimental infection of animals and the transmisison by insects, and the means of propagation of the disease from man to man is now known to be the sand fly, various types, probably, but certainly the *P papatassi* for one, while the possibility of transmission direct by *Musca domestica* is doubtful but very probable

A great deal of work has been done on this disease by Wenyon and others and has been referred to already

Epidemiology

The disease is endemic in certain well defined localities and occurs sporadically also in many parts of the world Three points stand out clearly that it has a tendency to seasonal incidence, being generally commonest in the late summer or early autumn, that the sores occur almost exclusively on exposed parts of the body, and that injuries or abrasions seem to determine the position of sores in many cases The sores, of course, only occur as fresh infections in places where there are more or less eastern conditions and where sand flies abound, apparently this presence of sand flies is essential

Geographical Distribution

In India the distribution tends to be markedly different from that of kala azar being almost invariably to the west of the Gangetic provinces where kala azar is so common It is in the dry and sandy areas rather than in the closely populated moist and tree covered portions so specially noted for kala azar that *L tropica* is found Although dogs can be artificially infected with *L tropica*, there is not in India much natural canine infection In Turkestan however there is an interesting instance of canine infection with both the local disease and with visceral as well whether this is the one infection or both still defies definition The same appears to be the case at various points around the Mediterranean The American disease espundia may be a source of some confusion as the mucocutaneous lesions which only occur even in the most infected areas in some 15 to o per cent of cases leave about 80 per cent with only the chancre which appears indistinguishable from the localized form recognized as *L tropica* elsewhere and which might be mistaken for it in regions where espundia exists

Transmission

The existence of a flagellate stage in culture the fact that infection is nearly always on exposed parts of the body and that the disease shows a marked seasonal incidence all point to the probability of transmission from man to man by an insect vector Patton proved that the parasite might be taken up by the bed bug if the latter were fed on the skin around the sores and that development might take place up to a flagellate stage in that insect but as Wenyon has pointed out this is probably no more than a case of culture going forward in the alimentary canal of the insect and quite unconnected with actual transmission of the disease by the bed bug

Domestic flies possibly may act either by direct transference of infective material from man to man on abraded surfaces or by ingestion of the parasites and the introduction of their feces into excoriations This was Laveran s theory and appeared when first expressed by him very likely to be the true one The infection is now known however to be transmitted in great part by the sand fly after undergoing a phase of development and a movement towards the proboscis in that insect

Laveran's theory may, in certain cases, be true also, just as the direct carrying of the infection to other sites near the original one by the fingers may be true also, but the transmission from man to man is undoubtedly by means of the sand fly and particularly by the *P papatassei* Wenyon[36] himself showed that development could take place in *Stegomyia* mosquitoes fed on and around the sores, and he showed also in 1911 that there was a great deal of evidence to suspect flies of the *Phlebotomus* type The observations of Sergent, Parrot, Donatien and Bequet[6] (1921) already referred to, is well as those of many others now prove conclusively that *L tropica* is spread by the sand fly, *P papatassei*, and perhaps by other types of sand fly as well

Pathology

There is a marked similarity between the pathological characters of oriental sore in its local manifestations and the generalized lesions of kala azar especially in the type of mononuclear cell mobilized at the site and its great accumulation of parasites in the cytoplasm

If the whole sore is excised, cut across and examined, the anatomical features are briefly as follows, (1) a central area of necrosis (2) a layer of disintegrating tissue and cellular infiltration, (3) a zone of granulation tissue in the cells of which parasites can be found in large numbers and (4) outside the third zone the tissues pass gradually through stages of diminishing congestion to their normal condition The impression given is that of a circumscribed new growth affecting the skin, the central parts of which have broken down as a result of interference with the capillary circulation Sections show that the effect of this type of Leishmania parasite on the invaded tissues is very similar to the effects of the parasite of kala azar, due allowance being made for the difference in the structures involved The essential phenomenon noted is the presence of large uninucleated cells of a type rarely found in normal skin, although common in the reticuloendothelial tissues, within which the parasites are to be seen in large numbers These cells so numerous as to give in the outer zone of the lesion the impression of an almost continuous layer of new tissue of embryonic type are often spoken of as macrophages but it appears probable that here as in kala azar they represent proliferated cells originating perhaps, from the endothelia of blood capillaries and lymph channels and spaces

These cells together with the cellular infiltrations associated with the inflammatory reaction on the one hand and the disintegrating tissue resulting from capillary stasis on the other constitute the characteristic features of the sections of an oriental sore Detailed descriptions are given by James H Wright[14] and by Laveran[1] Dogs and monkeys can be infected experimentally, and Laveran obtained interesting results by the inoculation of infective material into the testicles of mice The infection of dogs and monkeys as in man is strictly local In mice the parasites once established in the testicle may become generalized and infect the spleen and other organs



Fig 16 Early lesion in oriental sore leishmania parasites were very numerous in smears from the lesion

The Blood

As is to be expected in a strictly localized disease the blood changes are but slight There is no tendency to anemia and there is as a rule no leucopenia As in most protozoal diseases there is a tendency to an increase of the *large mononuclear leucocytes* at the expense of the *polymorphonuclears* Archibald[13] has described a marked increase of eosinophilic leucocytes in the sores themselves and their immediate neighborhood The parasites may be found sometimes after prolonged search in the peripheral blood close to the sore They are usually enclosed in leucocytes although occasionally they may be free in the plasma

DIAGNOSIS

The fully developed sore consists of a circumscribed loss of substance varying in size from that of a three-penny piece to a shilling or even larger affecting the epidermis and the skin and usually covered with an adherent scab formed from the serofibrinous discharge and from the disintegrated tissue This tends to bleed easily, if the scab is subjected to traction or is accidentally knocked or bruised (Figs 16, 17 and 18)



Fig 17 Oriental sore later stage of lesions

The whole area is raised and surrounded by a border of infiltrated and thickened skin and a zone of chronic inflammation which fades gradually into the normal tissue The ulcers are not, as a rule, painful, but they are intensely annoying as the least knock or injury leads to suffering, and flies persist in their attentions

The commonest situations are the hands, arms and face The sores are often multiple fresh crops appearing around the original lesion or on some other exposed surface It seems more likely that the secondary in

fections are caused by direct inoculation from the original sore rather than by the blood or lymph stream Lymph nodes seldom are involved the disease usually starts as a small papule or vesicle often attributed to the bites of flies or other insects This becomes inflamed enlarged and finally breaks down, gradually taking on the characters described above Richards and Fergusson [2] have described a wart like variety of cutaneous Leishmania in Egypt and Balfour and Archibald have called at-



Fig 18 Oriental sore stage of lesion still later than shown in Fig 17

tention to a non ulcerating type found by them in the Sudan A non ulcerating type has been described also in the Mediterranean basin and in India and elsewhere

Complications

Staphylococci streptococci diphtheroid bacilli and other secondary invaders tend to exploit the injured and ulcerated skin lesions and as a result erysipelatous attacks and lymphangitis have been noted On the whole it is remarkable how seldom oriental sore is complicated by serious bacterial infections although secondary organisms always are demonstrable on the ulcerated surfaces and in the discharge

Duration and Prognosis

The duration appears to vary according to locality the sore healing in a few weeks in some places and yet persisting for 18 months or more in others The ultimate prognosis is, of course good, but great disfigurement may result from lesions situated on the face

Healing usually accompanied by the formation of scar tissue seems to follow the death of the parasites which in turn, is probably the result of a slow process of auto immunization That some immunity follows these lesions seems certain, since recurrences are rare, once the sores have healed

The inhabitants of Bagdad induce sores on the legs as a means of warding off the disfiguring infections of the face so common in that locality Animal experiments tend to show that there is a period of hypersensitivity during and immediately after an attack, this being followed by some degree of immunity later on Such immunity, however, can only be demonstrated for a short time after the healing of the sore

Treatment

For the warty forms and at early stages, complete excision offers the best chance of thorough and speedy cure Broome's[38] method of freezing with carbonic acid snow, as used by its author and by Mitchell[39], has given good results The sore and the subjacent tissues are frozen by an application lasting from 5 to 30 seconds according to the size and depth of the lesion, the applications being repeated if necessary, several times at intervals of from 10 to 14 days Less severe methods, which have been reported on favorably are the use of x-rays by Easton[40] and the application of a pomade consisting of equal parts of methylene blue vaselin and lanoline as recommended by Cardamitis and Melissides

Leishmania tropica, it appears can often be destroyed, like *L donovani*, by the intravenous inoculation of tartar emetic, but there is of course a slight element of danger in this treatment, which makes it not worthwhile for an illness which is curable by simpler methods or by spontaneous recovery Great things were expected when the pentavalent antimony compounds were introduced On the whole however, these have proved far less applicable to *L tropica* than to kala azar, although

it has been shown that a course of neostilbin often is successful *Fouadin*, *too a pentavalent antimony preparation*, although less valuable for the treatment of kala azar than many others is said to be very effective in *L tropica* It is a sodium antimony pyrocatachin sulphate and is given in a solution of 6 3 per cent in doses of 1 5 c c increasing to 5 c c intramusculary On the whole however the local treatments above described are to be preferred

ESPUNDIA

Geographical Distribution

The mucocutaneous ulcerative disease of Brazil Peru and other parts of Central and South America called *according to locality espundia* bouba forest yaws Bauru ulcer and pian bois was proved in 1909 by Lindeberg and others to be due to a leishmania parasite indistinguishable from *L tropica* and *L donovani* Among the pioneers of this discovery were Carini and Piranhos[1] and Nattan Larrier Touin and Heckenroth[12] The parasite was proved to develop into the flagellate form by Pedroso and DaSilva in 1910 The disease has been reported from *British Dutch and French Guinea and from Brazil Venezuela Chili* Bolivia Paraguay Uraguay the Argentine and other places in the southern Americas It was in this disease that Vianna [4] in 1913 first tried antimony tartrate with success thus starting the treatment of kala azar on the valuable line that was taken up by Rogers and others and becoming the parent of the pentavalent antimony compounds now being used with increasing effectiveness

Symptomatology

Like oriental sore the initial lesion is most common on exposed parts such as the skin of the hands and arms the face and the lower extremities The skin lesions although they may be very severe and even fatal especially in the macrotubercular type tend as a rule to run a course comparable to that of oriental sore and ultimately to heal A sinister feature of the disease *however is that the initial lesion which has been*

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called the "chancre" of espundia, may be followed, some months or years after it has healed, by a secondary ulceration of the mucous membrane of the mouth or nose or both. These ulcers take a very serious course and are intensely resistant to all ordinary methods of treatment. They give rise to grave lesions of the mouth and nose, disfigurement of a kind that renders the sufferers repulsive in appearance with horrible fetor of the breath and a sequence of changes which render life almost intolerable. The end is caused usually by bacterial infections, the commonest being either septic bronchitis or bronchopneumonia.

How the mucocutaneous lesions are produced as a sequel to the initial sore is not yet quite clear but they occur in the more southerly parts of the Americas in from 15 to 20 per cent of cases known to have had the initial ulcers of the disease. During the interval between the occurrence of the chancre and the nasopharyngeal lesion the patient may have been in apparently normal health. Film examinations have, apparently, been negative including infection of the blood stream. It must be assumed therefore that the organism must find a place remote from blood examination to lie up in during the interval. Whether the infection reaches the mouth and nose from the original sore by contaminated fingers, towels or sponges, or whether it travels to the new site along the lymphatics or through the blood stream is not yet known, but the long interval suggests that it passes from one place to another by means of the circulation. Christopherson[68] reported several cases from the Anglo-Egyptian Sudan in 1913 and 1917 and Kirk[69] has treated a fair number of cases there in recent years but the latter raises the question whether the diagnosis can be made in the absence of a precedent ulcer or localized leishmanial infection which has not, so it appears, been found in these Sudanese cases. It is therefore still a question whether the two diseases are the same but a reference to Christopherson's paper[68] and his illustrations is calculated to convince the reader that they are either identical or very closely related.

Transmission

The infection is related to forest life, the cases occurring among those whose occupation involves work in the woods and near forest water courses or ponds. The epidemiological evidence points strongly in this disease as in the others to transmission by a blood sucking fly or

insect and *P intermedius* is under definite suspicion The treatment by tartar emetic introduced by Gaspar Vianna[24] for this disease and the pentavalent antimony preparations especially fouadin have deprived it of the terrors which lay in the path of those developing the secondary mucocutaneous syndrome

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CHAPTER XXXVI-A

TOXOPLASMOSIS

By HENRY PINKERTON

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Definition —A recently recognized general infection caused by a protozoon *Toxoplasma* The acquired form of the disease may be an acute fatal febrile illness with evidence of interstitial pneumonia mild encephalitis and a cutaneous eruption or the infection may be asymptomatic The congenital form of the disease in infants is an acute or subacute granulomatous encephalitis with acute chorioretinitis often terminating fatally during intrauterine life or a few weeks after birth In infants and children surviving for longer periods the disease as sumes a chronic or latent form characterized by healed retinitis cerebral calci fication hydrocephalus convulsions and mental retardation

HISTORICAL

First seen in Java sparrows by Laveran[1] in 1900 later by Splendore in rabbits and by Nicolle and Manceaux in an African rodent the gondi toxoplasma infec tion is now known to occur not infrequently in lower animals of several species *including the dog*

Early suggestions by Castellani by Fredorowitz and by Chalmers and Kamar[6] that toxoplasma infection might be related etiologically to certain cases

of splenic anemia were supported by meager evidence The first proof that toxoplasma is pathogenic for man was furnished by Wolf, Cowen and Paige in 1939 These workers definitely associated the organism with a type of granulomatous encephalitis in the new born infant and transmitted the disease to experimental animals In only two other instances has morphological evidence of the presence of toxoplasma in tissues been combined with evidence of transmission to animals One of these was an acute encephalitis in a six year old boy, reported by Sabin[8], and the other was a peculiar acute infection in an adult with a clinical picture of atypical pneumonia reported by Pinkerton and Henderson[9]

In five other reported cases of infantile or neonatal encephalitis[10] and in two other cases of adult infection[9,11] the diagnosis of toxoplasmosis has been established beyond a reasonable doubt by the demonstration of the organism in tissues In one other non fatal case of encephalitis in a child a probable diagnosis was made[8] by animal inoculation alone The clinical and pathological similarity of the cases diagnosed by tissue examination alone to those in which additional evidence was obtained by animal inoculation further supports the belief that all ten of the cases mentioned above were actually toxoplasmosis

Toxoplasma in human tissues was for a time confused with another organism, *Encephalitozoon cuniculi* but it is believed that the former can be distinguished morphologically from the latter and from all other organisms of comparable size and shape in well stained film preparations or paraffin sections The differential morphological diagnosis of the organism is discussed in detail by Pinkerton and Weinman[11]

Incidence

Twenty eight proven cases of the congenital form of the disease, some published and some unpublished, have come to the attention of the author A number of these have been discovered by reviewing the slides of cases in which necropsy was done as long as ten years ago It is probable that this form of the disease is not rare and that it is often unrecognized

The acquired type of the disease in the symptomatic form is represented at present by only six proven cases but is undoubtedly of more frequent occurrence than these figures would indicate It is necessary to assume that the mothers of all children having the congenital form of the disease have an inapparent or latent infection, since no other hypothesis explains the presence of well developed lesions in the infants at the time of birth The true incidence of asymptomatic infection in the general population cannot be determined until reliable serological tests are made available

Although the great majority of reported cases have occurred in the United States cases have been reported from Holland Czechoslovakia, Brazil and Peru

Etiology

Toxoplasma is a protozoon of rather characteristic appearance The organisms are usually crescentic or pyriform in shape occasionally oval or rounded and in film preparations measure 5 to 7 microns in length by 1 5 to 4 0 microns in width (Fig 1) They have a definite nucleus which occupies the greater part



Fig 1 *Toxoplasma* as seen in giemsa stained film omentum of a guinea pig The strain of toxoplasma was obtained originally from an adult human case of acquired toxoplasmosis by intraperitoneal injection of blood into a guinea pig Note size of organisms as compared to that of red blood cells in the same field Magnification 1,000 diameters

of their width and usually is near the more pointed end of the organism In giemsa stained smears the nucleus and cytoplasm stain purple and blue respectively and give approximately the same color reactions as do lymphocytes In sections the organisms appear somewhat smaller and the true elongated shape of the organism is not often seen because most forms are cut transversely Crescentic forms arranged symmetrically in pairs suggesting recent binary division are seen often in smears and occasionally in sections

The taxonomic status of the organism is uncertain It has been classed with the sporozoa but it seems best to await more detailed study of its life cycle Morphologically the organism resembles certain forms of avian malarial parasites Present evidence favors the view that strains of *Toxoplasma* of human origin are biologically and immunologically identical with those of animal origin[1]

Epidemiology

The mode of transmission has not been established Humans doubtless are infected sporadically from a reservoir in lower animals In several instances[10] the mothers of infants with congenital infection were shown to have had contact with sick dogs or cats and a similar history of exposure to a sick cat was obtained

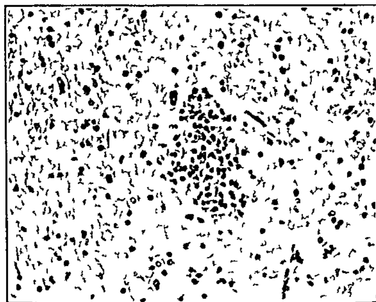


Fig 2 Focal lesion in cerebral cortex of acquired toxoplasmosis in an adult human. Magnification 225 diameters

in one case of acquired infection in a child[8] The occurrence of the neonatal form of the disease in a well developed state at birth can only mean that it is acquired in utero Since the mothers of the affected infants have been in good health it is necessary to assume that they are infected latently This is not difficult to believe in view of the fact that latent or inapparent toxoplasma infection is common in lower animals The mechanism of transmission of the infection from latently infected mothers to fetuses is not clear Infection could be acquired if lesions were present in the placenta, or if organisms were present in the amniotic fluid

Insect transmission seems not unlikely by analogy with other protozoal infections In two of the reported adult cases circumstantial evidence in favor of tick transmission was presented[9]

Experimentally the disease can be transmitted by all of the usual routes of

inoculation and by the oral and intranasal routes[18] The presence of infected cells in alveoli and bronchioles in human cases makes droplet transmission appear as a theoretical possibility The epidemiology and mode of transmission can be determined only by further study of additional cases as they are recognized and by experimental work



FIG 3 Heart muscle from acquired human case of toxoplasmosis Note one muscle fiber distended with huge number of protozoa and another containing a small number Magnification 400 diameters

PATHOLOGY

In the congenital form of the disease the outstanding pathological feature is a granulomatous encephalomyelitis Grossly the brain and spinal cord show yellowish or white necrotic foci ranging from the limit of visibility up to several millimeters in diameter Similar granulomatous lesions in the choroid and retina result in the appearance of multiple raised edematous pigmented areas In the more chronic cases healing of the granulomatous lesions leads to multiple areas of intracerebral calcification (Fig 7) The chorioretinitis also assumes a less active appearance with atrophy and deep black pigmentation (Fig 6) Microphthalmos is common Internal hydrocephalus is almost constant and is

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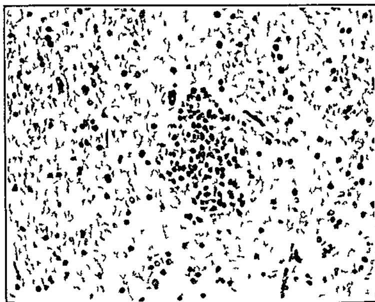


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in the central nervous system are much less conspicuous than in the congenital type, being few in number and microscopic in size These lesions resemble more those seen in typhus, spotted fever and in the virus encephalitides (Fig 2) Organizing interstitial pneumonitis with rounding of the alveolar lining cells a gelatinous alveolar exudate and the formation of hyaline membrane (Fig 5)



FIG 5 Section of lung from adult human case of acquired toxoplasmosis showing gelatinous exudate hyaline membrane formation and interstitial pneumonitis Magnification 250 diameters

appears to be a conspicuous feature Protozoa are seen distending the alveolar lining cells histiocytes in the alveolar walls and phagocytic cells lying free in the alveoli (Fig 4) Except for the presence of the organisms the picture greatly resembles that described in certain atypical pneumonias [4] The resemblance to the virus infections namely the occurrence of interstitial lesions in the lung and brain is believed by the author to be explained by the fact that *Toxoplasma* like the viruses develops as an obligate intracellular parasite

Granulomatous necrotic foci ranging from microscopic size up to 0 5 cm in

caused by mechanical obstruction in the process of healing as in other types of encephalitis Granulomatous necrosis in the walls of the dilated ventricles usually is present and this tends to enlarge the ventricles still further The etiological organism, *Toxoplasma* is found in large numbers in the lesions in the cen



FIG 4 Phagocytic cell in alveolus from lung of an adult human case of acquired toxoplasmosis Note large number of parasites in phagocytic cell Magnification 1 600 diameters

tral nervous system and in the retina Other lesions occasionally found outside of the nervous system and eye are splenomegaly, hepatomegaly and a maculopapular cutaneous eruption Interstitial pneumonitis caused by toxoplasma has been reported in only one infant Granulomatous lesions and organisms are seen occasionally outside of the nervous system, notably in the myocardium, but this generalized involvement is less striking than in the acquired form of the disease

The pathological picture of the acquired form of the disease can be described somewhat less confidently because only a few cases have been reported Lesions

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Granulomatous necrotic foci ranging from microscopic size up to 0 5 cm in

diameter are commonly present in one or more of the following organs heart, liver, spleen adrenals, lymph nodes and skin *Toxoplasma* organisms are found in these focal lesions and also with great regularity in myocardial fibres, even in the absence of focal lesions (Fig 3)

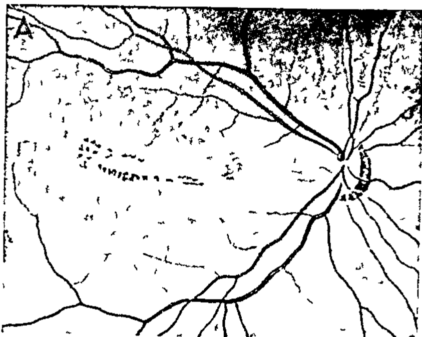


Fig 6 Toxoplasmic chorioretinitis showing beginning pigment action and atrophy Photograph of drawing of eyeground (Courtesy of Doctors Cowen Wolf and Paige[10])

Clinical Picture

The *congenital form* of the disease presents a fairly constant, characteristic and well recognized clinical picture varying somewhat with the acuteness of the disease and modified in some cases by apparent recovery with residual permanent damage to the central nervous system and eyes

In the acute and subacute cases symptoms and signs of the disease are present at birth or develop shortly thereafter In one case hydrocephalus was present in such degree as to necessitate craniotomy Convulsions, fever and hydrocephalus of variable extent usually give the first evidence of the disease Bilateral focal chorioretinitis involving the macula (Fig 6) is almost constant Microphthalmos, ocular palsies tremors twitching and spastic paralysis are often present Intracerebral calcification (Fig 7) may or may not be present at this stage Less constant signs are jaundice a maculopapular cutaneous eruption, interstitial

pneumonitis anemia leukopenia splenomegaly and hepatomegaly The spinal fluid usually is xanthrochromic with high protein content and increased cells ranging up to 1 500 lymphocytes and erythrocytes predominating *Toxoplasma* organisms may be found in the sediment of the spinal fluid in considerable numbers The mortality from this acute or subacute type of the disease is high



FIG 7 Roentgenogram showing multiple foci of intracerebral calcification in 2 year old child with congenital toxoplasmosis (Courtesy of Doctors Cowen Wolf and Paige)

In cases surviving beyond infancy the disease assumes a latent or at times a healed form The demonstration of organisms in the spinal fluid in one such instance indicates that apparent recovery with persistence of organisms in the body is possible Such children may survive through childhood with fair general health The outstanding features of this latent form of the disease are poor vision healed chorioretinitis strabismus nystagmus microphthalmos intracerebral calcification chronic hydrocephalus mild mental deficiency retardation of speech development and epileptiform convulsions or petit mal attacks

The clinical picture of the *acquired form of the disease* at present cannot be given categorically In two cases occurring in adults the picture was that of an obscure febrile illness beginning with a dry hacking cough and developing clinical and x ray evidence of an atypical pneumonia A striking feature was the

rapid development of dyspnoea and cyanosis, which was more severe than would have been expected from the appearance of the x ray plate One patient showed a positive Oppenheim reflex but evidence of central nervous system involvement was not impressive A cutaneous eruption resembling that of the typhus spotted fever group of diseases was observed in these two cases while in a third case[11] cutaneous lesions containing many protozoa were found post mortem In this third case the clinical picture was obscured by the presence of a concomitant bartonella infection

The two *cases in children* reported by Sabin[8], probably are to be regarded as of the acquired type In these cases the outstanding features were headache convulsions and a spinal fluid containing a few hundred mononuclear cells As in the adult cases the neurological findings were not striking One of the cases recovered after a brief illness of three days' duration, while the other died on the thirtieth day Clinical evidence of pulmonary involvement was absent in both cases but the necropsy in the fatal case was confined to the brain and spinal cord Cutaneous eruption was not observed in either of these cases

Diagnosis and Differential Diagnosis

Definite diagnosis at necropsy can be made on the basis of the pathological picture already described with the finding of *Toxoplasma* organisms in tissue sections sufficiently well stained to allow their identification The diagnosis is supported further by the successful transmission of the disease to experimental animals

Definite diagnosis during life has been made in at least five cases by the demonstration of the organisms in spinal fluid or biopsy material or by the transmission of the disease to animals The possibility of spontaneous *Toxoplasma* infection in the animals employed must be ruled out The recommended procedure is injection of the suspected material, blood cerebrospinal fluid sputum or biopsy material intracranially into mice and intraperitoneally into guinea pigs Control animals should be injected with similar material from cases not suspected of suffering from toxoplasmosis

In the congenital form of the disease the clinical picture as described above is so characteristic that the diagnosis may be made with considerable assurance on this basis alone The important features are the characteristic retinal lesions, evidence of hydrocephalus cerebral calcification convulsions and the spinal fluid picture The diagnosis is strengthened by a positive complement fixation test and by the demonstration of neutralizing antibodies

Since nearly all of the signs and symptoms of congenital toxoplasmosis may be found individually in other diseases, the differential diagnosis must include

these conditions Congenital malformation of the brain non toxoplasmic hydrocephalus, non toxoplasmic forms of retinitis idiopathic mental deficiency and epilepsy cerebral calcification from other causes and tuberous sclerosis must be considered

It has been demonstrated that toxoplasma infection may cause retinitis hydrocephalus epileptic seizures etc The frequency of toxoplasma infection as a cause of these various conditions can be determined only by further study and conservatism is indicated in making a diagnosis of toxoplasmosis in the absence of morphological evidence or evidence obtained from animal inoculation

Diagnosis of the acquired type of the disease can be made with certainty only by demonstrating the *Toxoplasma* organisms or by transmission of the infection to animals in an unequivocal way The clinical picture of acquired toxoplasmosis may in the light of present evidence be confused in adults with diseases of the typhus spotted fever group typhoid fever atypical or virus pneumonia and probably with other acute infections In children the disease must be differentiated chiefly from other types of non suppurative encephalitis and accurate diagnosis requires careful laboratory study

Warren and Sabin[15] recently have obtained results of an encouraging nature in an attempt to work out a reliable complement fixation test for *Toxoplasma* infection using an antigen prepared from infected rabbit brain Sabin and Reichman[15] find that neutralizing antibodies may develop early in the course of experimental toxoplasmosis in monkeys Both the complement fixation and the neutralization test must be carried out on fresh serum or on serum stored in the frozen state In six cases of congenital toxoplasmosis[10] the neutralization test was found to be uniformly positive and in two of these cases positive reactions were obtained also with serum from the mothers of the affected children Serological tests are difficult of interpretation and have not yet reached a stage of development where they have more than confirmatory diagnostic value

Treatment and Prophylaxis

In general treatment should be supportive and symptomatic In the congenital form of the disease hydrocephalus and convulsions should be treated independently of their etiology Dyspnoea and cyanosis in the acquired form of the disease should be treated by oxygen administration Sulfanilamide in moderate doses had no apparent beneficial influence in two cases of acquired toxoplasmosis but Sabin and Warren[16] recently have presented evidence that sulfapyridine and sulfathiazole may affect favorably the course of the experimental disease in the rabbit even if not given until symptoms have developed Sulfanilamide was found to be less effective than sulfapyridine and sulfathiazole

Present epidemiological knowledge does not suggest effective methods of prophylaxis The development of reliable serological tests for latent infection in pregnant women may lead eventually to methods for the prevention of the congenital form of the disease

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March 1 1944

CHAPTER XXXVII

DISEASES CAUSED BY TREMATODES OR FLUKES

By DONALD L AUGUSTINE

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INTRODUCTION

The parasites frequently called trematodes or flukes are members of the class *Trematoda* in the phylum *Platyhelminthes* All trematodes are true parasites Many attach themselves to superficial parts of the host while others enter the host and inhabit the internal organs. The former are called ectoparasites and the later endoparasites Ectoparasitic forms develop directly on and occasionally within, a single type of host and are known as *monogenetic* trematodes They are, for the most part, parasites of aquatic vertebrates, and some species are of great economic importance in fish hatcheries. None of the monogenetic trematodes parasitizes man Endoparasitic forms have complicated life cycles with development always through a sequence of young individuals unlike the parent and require at least one and sometimes more

than one change of host They are said to be *digenetic* All species infecting man are digenetic trematodes

Trematodes are bilaterally symmetrical animals with unsegmented bodies. Many are flat and leaf-like, but the majority are long, narrow and oval in cross section Most digenetic trematodes are less than 30 mm long, but *Fasciolopsis buski*, the largest species infecting man may attain a length of 75 mm and a breadth of 20 mm At the other extreme *Heterophyes heterophyes*, the smallest trematode of man never exceeds 2 mm in length and 0 7 mm in breadth

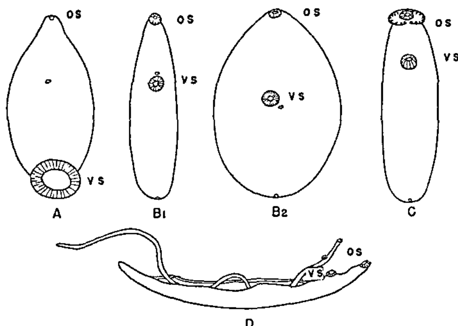


Fig 1 Schematic presentation of the external appearance of the main types of trematodes parasitizing man A an amphistome B1 and B2 distomes C an echinostome D schistosomes (male and female worm *en copula*) os oral sucker vs ventral sucker

Adult trematodes parasitizing man are recognized by the nature of the adhesive or hold fast organs two cup shaped suckers One of these encircles the mouth at the anterior tip of the body and is called the oral sucker The second sucker which may be larger or smaller than the first occupies a position somewhere on the ventral surface If located far back on the body it is called the posterior sucker otherwise it is said to be the ventral sucker or the acetabulum Adhesion generally is

affected by the ventral or the posterior sucker, although the oral sucker may also assist

Distinctive types can be recognized by means of the external characters namely body shape and the character and position of the suckers Thus, amphistomes distomes, echinostomes and schistosomes are types of trematodes infecting man (Fig 1) Amphistomes have a thick, fleshy body provided with a well developed posterior sucker Distomes have the ventral sucker somewhere on the ventral surface, frequently close to the oral sucker but not at the posterior end of the body The ventral sucker of an echinostome is also on the ventral surface and close to the oral sucker but the oral sucker is surrounded by a spinous collar the distinguishing character The schistosomes are unisexual blood flukes with long and slender bodies well suited to life in blood vessels Most of the trematodes infecting man are distomes The internal structures must be taken into account before specific diagnosis can be made The general structure of a typical trematode parasitizing man is schematized in Fig 2 Special fixation and staining technics must be employed to demonstrate the internal structures

The body of a trematode is covered with a non cellular, tough, elastic layer the cuticle, which may be either smooth or embedded with backward pointing spines or scales Trematodes, unlike the nematodes or round worms, have no body cavity, the internal organs being enveloped in a spongy packing tissue, the parenchyma, which consists of a network of cells and fibrils with irregular cavities in its meshes In some trematodes the body is very muscular which renders it opaque In others the muscles are so weakly developed that the body is quite transparent and the larger, more prominent internal structures clearly show in shadowy relief Generally, muscle fibrils are arranged in layers immediately beneath the cuticle These include (1) an outermost layer of cuticular fibrils (2) a middle layer of diagonal fibrils and (3) a layer of innermost longitudinal fibrils Additional vertical muscles traverse the parenchyma especially in the lateral fields where the internal organs do not interfere with the arrangement The nervous system consists of two main clusters of nerve cells or ganglia linked by a wide transverse commissure forming a rudimentary brain located above the intestine Three pairs of nerves generally leave the front of the brain, and their numerous branches supply the oral sucker and adjacent parts Three pairs of longitudinal nerves also leave the hind part of the brain to supply various regions of the body Apparently these are mostly motor nerves,

since special sensory structures are lacking The excretory system is composed of a system of fine canals and finer branches each of which terminates in a special kind of cell called a flame cell The flame cells appear characteristically in groups and their pattern is of taxonomic value especially in the larval stages where it is simple[1] The excretory bladder is located in the median line in the posterior part of the body and opens through the excretory pore located at or near the posterior end of the body

The digestive system commences at the anterior tip of the worm with the mouth which is surrounded by the oral sucker Its location is generally terminal or slightly subterminal From the mouth the oral cavity leads backward into a muscular pharynx which is more or less globular and usually is smaller in diameter than the oral sucker A short pre pharynx may appear in some cases between the oral sucker and the muscular pharynx Usually a very short narrow tube with muscular walls the esophagus, connects the pharynx with the intestine These structures of the so called foregut' are lined by a continuation of the cuticle covering the body The esophagus opens into the intestine which generally consists of two elongate blind ceca or crura running backward which vary in length according to the species The intestinal crura are lined with tall cylindrical epithelial cells and have a weakly developed muscular layer Most species have no

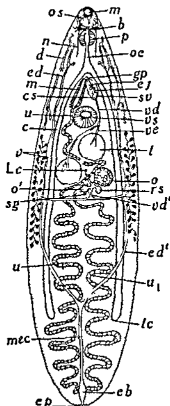


Fig 2 Schematic presentation of the chief organs and vital systems of a typical digenetic trematode (after Dawes) b brain c cecum cs cirrus pouch d excretory ductule ed excretory duct ej ejaculatory duct ep excretory pore eb excretory vesicle gp genital pore Lc Laurer's canal and pore m mouth m metraterm mec median excretory canal n ventral nerve o ovary o ootype os oral sucker p pharynx rs seminal receptacle sg Mehlis gland sv seminal vesicle t testis tc termination of caecum u uterus u descending limb of uterus v vitellaria vd vas deferens vd vitelline duct ve vasa efferentia vs ventral sucker

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Masses of germ cells known as germ balls proliferate within the mother sporocyst and develop either into second generation sporocysts or into more complex organisms called rediae. Other germ balls then proliferate within the second generation sporocysts or rediae (according to the species) giving rise to tailed larvae, cercariae, which escape from the snail and swim about. Cercariae may directly infect the definitive host by penetrating the skin, as do schistosome cercariae, but the cercariae of most species encyst on herbage or within food animals and passively enter the human host through the ingestion of such parasitized food. Such an encysted cercaria is called a metacercaria. The main features of the life histories of some of the commoner and more important trematodes of man are outlined in Table I.

TABLE I

LIFE HISTORIES OF SOME TREMATODES INFECTING MAN

Early larvae in snails, cercariae leave this host and	Penetrate the skin	*Schistosoma mansoni* (man) *Schistosoma haematobium* (man) *Schistosoma japonicum* (man, dog, cat, rat, cattle, horse)
	Encyst on herbage	*Fasciolopsis buski* (man, swine) *Fasciola hepatica* (ruminants, man)
	Encyst on or within same snail or another snail	*Echinostoma ilocanum* (man, rat, dog)
	Encyst in or on Crustacea	*Paragonimus westermani* (man, felines)
	Encyst in fresh water fishes	*Clonorchis sinensis* (man, felines) *Heterophyes heterophyes* (man, felines) *Metagonimus yokogawai* (man, felines, pelican) *Opisthorchis felineus* (man, felines)

anal opening, the waste products from the intestine being discharged through the anterior opening which functions as both mouth and anus. The food of trematodes consists of blood and epithelial cells, plasma and lymph, intestinal contents of the host and inflammatory products, according to the species of trematode and its position in the host.

Most trematodes are true hermaphordites, but in one group, the schistosomes, the sexes are distinct. In the hermaphorditic forms the male and female systems generally open close together in a shallow pit or genital atrium which usually occupies a median position between the oral and ventral suckers. The male system consists of a pair of testes, vasa efferentia and a vas deferens which passes into a structure known as the cirrus pouch. The cirrus pouch encloses (1) a dilated portion the seminal vesicle (2) unicellular prostate glands and (3) a terminal muscular portion which is an eversible and protrusible tube, the cirrus which functions as the male organ of copulation. The testes may be spherical, globular, lobed, branched or ramified and may lie side by side or one in front of the other, posterior to the ventral sucker and usually posterior to the ovary.

The components of the female reproductive system are a single ovary, oviduct, a seminal receptacle, paired multiple vitelline or yolk glands with their ducts, a glandular portion (Mehlis' gland) surrounding the muscular ootype, a canal (Laurer's canal) for the escape of excess shell forming secretion and the uterus, of which the terminal portion may be muscular and serves as a vagina. The ovary may be spherical, lobed or branched. It rarely occupies a medial position. In many instances the folds of the uterus are confined to the region of the body in front of the ovary within the central area, while the vitelline glands extend along the body lateral to the intestinal branches. The shape and position of the testes and ovary and the length and position of the uterus are of particular taxonomic value.

Eggs of hermaphroditic trematodes are oval and have a lid or operculum at one pole. They may or may not be fully embryonated according to the species, when they reach the external world. Upon reaching bodies of fresh-water the egg sooner or later hatches and the embryo, a ciliated larva, swims about in search of its host, always a fresh-water snail. This larva is called a miracidium. The miracidium may enter the snail by directly penetrating the soft tissues. Upon gaining entrance into the snail, the miracidium loses its ciliated covering and quickly becomes a simple, elongated saccular organism which is known as a first generation sporocyst or mother sporocyst.

DISEASES CAUSED BY BLOOD FLUKES (SCHISTOSOMIASIS)

Schistosomiasis is a group of diseases caused by trematodes of the genus *Schistosoma* Weinland 1858 which parasitize the vesical and pelvic venous plexuses They are commonly called schistosomes or blood flukes

Adult schistosomes are elongated unisexual dimorphic trematodes The female usually is longer than the male round in outline and is characteristically carried in a ventral groove the gynecophoric canal which is formed by ventrally flexed lateral outgrowths of the body of the male (Fig 1 D) The suckers are poorly developed The cuticle may be smoothed or tuberculated The muscular pharynx a prominent character for hermaphroditic trematodes is absent The esophagus is short the ceca long and united posteriorly to form a single cecum which ends blindly in the caudal extremity

The male reproductive system includes several testes (number and size vary with the species) located a little behind the ventral sucker The genital pore is located near the anterior end of the gynecophoric canal The ovary is situated in the posterior region of the body of the female worm *immediately in front of the union of the intestinal* branches The oviduct leads from the posterior pole of the ovary passes forward and soon is joined by the vitelline duct at the ootype The uterus extends forward from the ootype as a straight tube and opens through the genital pore located just behind the ventral sucker The vitelline glands occupy the posterior part of the body extending from the ovary to the caudal extremity

The female schistosome worm deposits her eggs in the small venules of the urinary bladder or the large intestine The eggs pass through the wall of the venule and must traverse a certain amount of tissue to enter the bladder or the lumen of the intestine in order to leave the body of the host with urine or feces

According to Kohlschutter and Koppisch[2] the egg first comes to lie against the endothelial lining of the venule in which it is laid Endothelial cells rapidly extend from all sides by multiplication and cover the egg competely thereby isolating it from the blood current An inflammatory reaction then develops about the egg and the venule is either pushed aside or is obliterated It is apparent that only the eggs deposited *immediately beneath the epithelium ever reach the outer world* to carry on the life cycle of the parasite The majority of the eggs are trapped

Since all the trematodes infecting man must depend upon fresh water snails for the completion of their life cycles, and because of the marked host-specificity of miracidia, the geographic distribution of a given trematode species is primarily restricted to the geographic distribution of its proper snail host Further limitations in distribution might be expected where a second intermediate host is involved However cercariae often show little or no host-specificity, and suitable secondary hosts are widespread The cercariae of the lung fluke, *Paragonimus westermani*, for example readily encyst in several species of fresh water crayfish and crabs and those of the liver fluke *Clonorchis sinensis*, are known to parasitize over forty species of fresh-water fish

Inasmuch as the majority of the various trematodes of man are acquired by consumption of particular plants, fish and crustacea (transfer agents) the distribution and incidence of infection are further related to diet and food habits *Clonorchis sinensis* occurs extensively throughout eastern China where it is a frequent parasite of the cat and dog but it occurs as a human parasite only in those localities where fresh water fish are habitually eaten raw or in an insufficiently cooked form The absence of indigenous lung fluke infection paragonimiasis in the human population of the United States can be attributed to the absence of raw crayfish from the diet

Within an endemic area the use of human excreta as a crop fertilizer and its insanitary disposal are always major sources of pollution of ponds and streams As a rule human infection, as well as infection in reservoir hosts is chiefly of human origin

The clinical manifestations of trematodiases depend largely upon the organ or tissues invaded and the number of worms present The intestinal trematodes usually do not produce striking lesions but marked local tissue reactions are characteristically provoked by adult trematodes in the liver and lungs which in extreme instances may result in extensive fibrosis of the organ In schistosomiasis or blood fluke infection the damage to the host is chiefly brought about by eggs in the tissues and not by the adult parasites in the veins In most cases the effects of trematode parasitism are progressive and in proportion to the intensity of infection resulting from reinfection

In a trematode infection a comprehension of the disease is dependent on (a) an understanding of the specific etiological agent, (b) the infective stage and its portal of entry into the body, (c) the migration of the larvae to the site where they become mature and oviposit and (d) the local and systemic reactions to the parasites and their products

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in the tissues where they provoke an intense inflammatory reaction with giant cell formation leading to their encapsulation and ultimate absorption or calcification The host cell activity varies in different individuals In some cases it is only mild while in others it may be pronounced

Schistosome eggs contain a more or less fully developed, heavily ciliated, miracidium when they leave the host If the eggs reach fresh water, the miracidium hatches within a few hours and attacks and enters an appropriate snail host Subsequent development in the snail occurs close to the point of entrance The ciliary coat is shed, and within 48 hours there develops an elongated, simple, thin-walled sac, a mother sporocyst The germ cells of the mother sporocyst form into daughter sporocysts which by the 18th day escape into the tissues of the snail and move into the terminal portion of the snail s body the digestive gland where they grow and give rise after about 6 weeks to the next stage in the life cycle the cercariae These cercariae have a forked tail with fureal rami less than half as long as the tail stem

Upon leaving the snail host the cercariae swim about and when they come in contact with persons wading bathing or working in the infected waters they attach themselves to unprotected parts of the skin by the ventral sucker Extensive penetration is not affected, however, until the person has left the water and the water begins to evaporate on the skin The tail of the cercaria is shed at that time

By the use of secretions of well developed penetration glands and the activity of the anterior organ of penetration, the cercariae pass through the skin and pass via the lymphatics to the right side of the heart and the lungs and then are carried with the arterial blood to all organs and tissues Those which reach organs and tissues with venous drainage by way of the portal vein continue their journey into the intrahepatic portal branches where they feed grow and attain sexual maturity The cercariae which fail to reach the hepatic portal vessels, are destroyed locally in the tissues in which they are caught Many fail to leave the pulmonary circulation

Upon reaching sexual maturity the worms leave the liver *en copula* and migrate against the venous flow of blood to the pelvic or the vesical plexuses according to the species involved A period of from five to twelve weeks may be required for complete development of the adult worms and for production of eggs

There are three species of schistosomes which mature in man, (1) *Schistosoma haematobium* (Bilharz, 1852) Weinland 1858 (2) *S mansoni* Sambon 1907, (3) *S japonicum*, Katsurada, 1904 At least six other-

species have been reported from man but evidence is insufficient to establish any of these as a human parasite[3]

Schistosomiasis Haematobia

Schistosomiasis haematobia is a chronic disease characterized by disturbances of the urinary system due to the presence of *Schistosoma haematobium* (Bilharz 1852) Weinland 1858 in the pelvic veins particularly those of the bladder The disease also is known as urinary schistosomiasis urinary bilharziasis endemic hematuria and red water

Epidemiology

The disease is widely spread throughout the tropical belt the eastern belt and north coastal areas of Africa and it occurs also in Palestine Syria Iraq Yemen Aden Protectorate Madagascar Mauritius Cyprus and Portugal It is prevalent in both Upper and Lower Egypt but Lower Egypt is the largest endemic area of the disease in the world In the United States the infection has been seen most frequently in African students coming from endemic areas and in persons particularly missionaries and army personnel who have had African or eastern Mediterranean residence No infections have been acquired beyond present known endemic areas

Schistosoma haematobium was first discovered in 1851 by Bilharz in Egypt Bilharz later established the relation between parasites and hematuria with the accompanying lesions of the bladder This work of Bilharz established for the first time a connection between a trematode parasite and a human disease Bilharz also made similar observations on *Schistosoma mansoni* in venules of the large intestine and rectum He did not however make a differentiation of species although two types of eggs were noted (1) with a terminal spine and ( ) with a lateral spine It was not until 1907 that the two species were definitely separated by Sambon the separation being based on (a) the position of the spine on the eggs, (b) the different anatomical habitat (c) differences in pathogenicity and (d) differences in geographic distribution Sambon retained the name *Schistosoma haematobium* for the urinary type with terminal spined eggs and established a new species *Schistosoma mansoni* for the rectal form with lateral spined eggs The morphological char-

TABLE II

DISTINGUISHING FEATURES OF THE HUMAN SCHISTOSOMES

	S. haematobium	*S. mansoni*	*S. japonicum*
Adult male	Size 1-14 mm long Cuticula finely tuberculated Intestinal crura unite late so that united region of intestine is short Testes large 4 in number	10-12 mm long Cuticula grossly tuberculated Intestinal crura unite early so that united region of intestine is long Testes small 8 in number	9-1 mm long Cuticula non-tuberculated Intestinal crura unite far back united region being one-fifth to one-sixth of body length Testes slightly lobate 7-8 in number
Adult female	Size 0 mm long Uterus long and voluminous and contains a number of eggs Ovary in posterior half of body	12-16 mm long Uterus short contains usually from 1-3 eggs at a time Ovary in anterior half of body	1-16 mm long Uterus well developed occupies about half of postacetabular region contains 50-300 eggs Ovary about the middle of body
Eggs	Terminal spine 150 x 60 usually deposited in veins of bladder escape with urine	Lateral spine 150 x 60 usually deposited in veins of rectum escape with feces	Abbreviated spine 80 x 65 deposited in portal system enter intestine higher than with *S. mansoni*
Intermediate hosts	*Planorbis dufourii* (Portugal) *Bulinus contortus* (North Africa Palestine and Iraq) *B. dybowskii* *B. brocchii* (North Africa) *Physopsis africana globosa* (West Central and South Africa)	*Planorbis (Biomphalaria) boissyi* (North Africa) *Planorbis (Biomphalaria) pfeifferi* *Planorbis (Biomphalaria) ruppellii* (West Central and East Africa) *Australorbis glabratus* (Dominican Republic Puerto Rico Brazil Dutch Guinea Venezuela) *Tropicorbis centimetralis* (Brazil)	*Oncomelania hupensis* (Yangtze River drainage system China along earth bank canals) *Oncomelania nosophora* (1 Southern two-thirds of China in ditches creeks in mountain valleys and along inner edges of rice fields 2 Honshu and Kyushu Islands Japan) *Oncomelania formosana* (Formosa) *Oncomelania quadrasi* (Philippine Island)

meters and life history data for *S haematobium* are given in Tables I and II

Pathology

The pathological changes in urinary schistosomiasis depend very largely on the intensity and duration of the infection The local lesions are due almost entirely to eggs deposited in the submucosa of the bladder and particularly to those which fail to leave the host The presence of the eggs in the tissue provokes a foreign body reaction of giant cells epithelioid cells and eosinophils which is followed by a peripheral fibroblastic proliferation (Fig 3) The bladder in the early stages shows



Fig 3 Bladder wall showing dense infiltration with eggs of *Schistosoma haematobium* many of which are calcified Low magnification (after Hutchinson)

diffuse reddening and swelling, while the impregnation of the mucosa with eggs results in the formation of minute tubercles Calcification of these tubercles leads to the formation of the so called sandy patches of the bladder These may fuse together and form a membrane which may slough and thus give rise to an ulcer Extensive ulceration usually is dependent on secondary infection[4] The formation of papillomata is a characteristic feature in schistosomiasis, which in some cases may undergo malignant changes[5] The bladder papillomata appear singly or in groups and are sessile dark red in color and yellowish at the tips, due to the presence of ova The size varies The surface is coarse, spongy or granular

It is exceptional for the lesions to be uniformly distributed throughout the bladder Pathological changes occur most frequently in the fundus trigone and around the ureteral openings In some instances the lower third of the ureter becomes involved, and obstruction occurs from the thickening of its wall Unless secondary infection occurs the upper ureter and the kidney are not affected The process may extend to the prostate the urethra and the seminal vesicles as well as to other pelvic structures Urinary schistosomiasis in later stages frequently is associated with urinary fistulae in the perianal region and at the base of the scrotum the tracts of which are lined with granulation tissue heavily charged with eggs of the parasite In case the adult worms lodge in the hemorrhoidal veins similar changes may occur in the rectum Infections of the rectum without bladder involvement have been observed a condition peculiar to some areas in Equatorial Africa

Eggs which fail to leave the venules are carried passively through venous channels to be deposited singly or in masses in the liver, lungs, spleen[6] and other aberrant sites where they provoke reactions similar to those in the urinary bladder and the intestinal wall Eggs lodged in the liver cause fibrosis in the periportal tissues Eggs deposited in the lungs obstruct the small arterioles pass through them and lie immediately outside them The tissue reaction around the eggs results in the formation of pseudotubercles Two types of lesion are produced, parenchymatous and arterial The parenchymatous lesions are in the bronchioles and alveoli They cause little alteration in the finer structure of the lungs The arterial lesions are more serious They are the result of the necrosis produced by the passage of eggs through the walls of the arterioles Necrosis is followed by healing with thickening and narrowing or occlusion of the lumina of the vessels The lesions may be focal

or diffuse resulting in dilatation and thickening of the arteries in the lungs and of the pulmonary artery and its primary branches The right ventricle of the heart dilates hypertrophies and finally fails The worms may be present also in the blood vessels of the lungs They appear to be harmless while living but when dead they produce a necrotic and focal pneumonia

Eggs lodged in the spinal cord give rise to miliary granulomas resembling those of tuberculosis In the skin they cause deep shot like pink papules which may occur singly or in clusters Skin lesions have been observed most frequently on the scrotum penis abdomen chest and lumbar regions In cases of prolonged and repeated infections the spleen becomes *greatly* enlarged and *fibrotic*

Clinical Manifestations

The earliest clinical manifestations are associated with the entry of the cercariae into the skin From 10 minutes to 3 hours after leaving the water annoying and persistent biting sensations may be felt over the parts of the body having been in direct contact with the infected water The skin of the feet legs hands and forearms are chiefly affected becoming congested inflamed and tender Minute petechiae may develop within the following few hours at the sites of invasion but these when present usually disappear after a few days unless scratched and secondary infection develops Severe and more persistent skin lesions may be due entirely or concurrently to infection with schistosome cercariae of non human origin (see Swimmer s Itch)

The first symptoms associated with the development of the parasites in the body may appear about 4 to 6 weeks after exposure The onset generally is gradual The patient may experience headache backache *lassitude fever with urticaria frequency of urination and terminal* hematuria[7 8] Bleeding may be accompanied by bladder irritation or may be entirely painless *Hematuria may continue indefinitely and for* years may be the only indication of the disease It may occur only once *a day or may be absent for weeks but characteristically it becomes more* regular and abundant as the symptoms of bladder irritability are established The urine characteristically is mixed with a thick sticky mucus, and the quantity generally is small In severe and advanced cases complicated by secondary infection the symptoms change to those of septic cystitis Hydronephrosis may be a late manifestation The clinical mani

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somiasis be strongly suspected even though no eggs can be demonstrated in the urine on repeated examination and the bladder appears normal on cystoscopic examination further search should be made for eggs in biopsy material" The only certain means of diagnosing pulmonary schistosomiasis is the presence of schistosome eggs in the sputum but actually they are rarely found in the sputum When pulmonary involvement is suspected the establishment of the presence of schistosomiasis is essential Eosinophilia is more marked in pulmonary than in other forms of schistosomiasis Intradermal and serological tests have been used for diagnostic purposes in schistosomiasis but these are in the experimental stage and cannot be relied upon at present for specific diagnosis

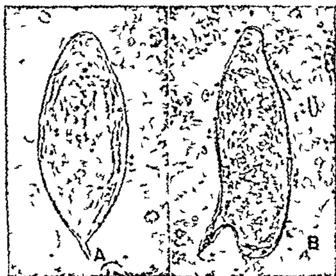


Fig 4 A Egg of *Schistosoma haematobium* in urine B Egg of *S mansoni* in feces x 4 0 (after van den Berghe)

Prognosis

Urinary schistosomiasis is probably seldom self limiting the parasites may live from 20 to 30 years or more Therefore the intensity and the duration of the infection are the important factors in determining the prognosis Most infections occurring in non residents in endemic areas are of a mild character Little or no discomfort is felt and the patient

festations in bronchopulmonary schistosomiasis include bronchial asthma, chronic bronchitis, bronchiectasis pulmonary emphysema and pulmonary fibrosis In the cardiovascular form the clinical picture is similar to that of primary pulmonary endarteritis (Ayerza's syndrome) except that cyanosis is absent in pulmonary schistosomiasis and appears only when the right ventricle has failed Right ventricular failure in schistosomiasis is late in appearance as its cause is mechanical rather than myocardial Mental confusion and paralytic symptoms, visual disturbances and appendicitis may arise from involvement of the central nervous system conjunctiva and the appendix

Diagnosis

In the majority of cases the diagnosis of schistosomiasis haematobia does not present any great difficulty Symptoms which may develop prior to egg production are nonspecific and there are no diagnostic laboratory procedures Aside from taking the history of the complaint, the diagnosis depends almost entirely on the discovery of terminal spined eggs in the urine (Fig 4, A) or the demonstration of the pathological changes in material obtained by biopsy The presence of hematuria in persons living or having had residence in endemic areas is always a suggestive symptom of the disease Urinary schistosomiasis is almost invariably caused by *Schistosoma haematobium* and rarely by *S mansoni* Peters Huntress and Porter[9] recently reported a case of urinary schistosomiasis in Portland Maine, in which both *S haematobium* and *S mansoni* were present The infection had been acquired in Palestine

For examination the urine should be passed into a sedimentation jar and examined at once macroscopically Any deposit such as blood pus or mucus should be noted Terminal hematuria is characteristic, and the bloody urine may be seen sinking to the bottom of the container Sedimentation for about one hour is sufficient A portion of the sediment then is transferred by means of a pipette, to a coverglass and examined microscopically for eggs of the parasites Having established the case as urinary schistosomiasis, careful and systematic examination of the bladder should be carried out to determine the severity of the disease[4, 8] Cystoscopy is of considerable value in determining the condition of the bladder or in arriving at a diagnosis when ova are not demonstrable in the urine However, direct inspection of the bladder frequently fails to reveal the existence of chronic schistosomiasis Should urinary schisto

Most infections in Egypt and the Eastern Mediterranean countries are acquired during the hot summer months The snail population is greatly reduced during the winter season Those which survive may retain their infections but the development of the asexual stages of the parasite is markedly retarded and few if any cercariae emerge Efforts to destroy the snail hosts by biological and chemical methods have not been successful Widespread application of antimony treatment for many years in Egypt has benefited sufferers with acute symptoms but has failed to stem an increasing tide of new cases Complete cures apparently are rare, and the rate of reinfection is high Since there are no natural reservoir hosts for the adult parasites and infection in the snail host is of necessity of human origin control of the disease lies in the prevention of contamination of bodies of fresh water with human excreta Radical changes in prevalent social conditions are necessary before this seemingly simple measure can be accomplished

Schistosomiasis Mansoni

Schistosomiasis mansoni is a chronic disease giving rise to dysenteric symptoms splenomegaly and cirrhosis of the liver caused by the presence of *Schistosoma mansoni*, Sambon 1907 in the portal system The disease is known also as intestinal schistosomiasis, intestinal bilharziasis and Manson s disease

Epidemiology

Africa northern South America and the Caribbean region are the great endemic foci Its distribution in Africa closely parallels that of urinary schistosomiasis but it is not endemic in North African countries including Tunis, Algeria and the Moroccos It is present along the East African coast from Zanzibar to the Zambezi River and in Madagascar In Central Africa it occurs throughout parts of French Equatorial Africa Belgian Congo Rhodesia and the Union of South Africa In West Africa it is present in Senegal French Guinea Liberia Sierra Leone Gold Coast Nigeria and the Cameroons In Asia a few indigenous cases have been reported only from Yemen and Palestine

Schistosoma mansoni is one of the very few trematodes of man which has become established in new areas It was introduced into the Americas

early consults a physician The prognosis is usually very good in these cases

Treatment

Antimony compounds, particularly sodium antimony tartrate and potassium antimony tartrate (tartar emetic), have been used for 30 years in the treatment of schistosomiasis Sodium antimony tartrate has been preferred in the past by many clinicians for intravenous injection Intra venous injections on alternate days of a freshly-prepared 2 per cent solution in sterilized water are recommended For adults the initial dosage of 0 06 gm (3 0 c c) should be increased to a maximum of 0 12 gm (6 0 c c) by the third dose and continued every other day for a period of 4 or more weeks until a total dose of 1 3 to 1 8 gm has been administered The patient should remain recumbent for at least an hour after administration of the drug

Fuadin a trivalent antimony compound, however, has become the drug of choice and now is generally recommended for the first trial in treatment Intramuscular injections of a 7 per cent solution are recom mended The first three doses of 0 105 gm (1 5 c c), 0 245 gm (3 5 c c) and 0 35 gm (5 0 c c) are given on successive days Seven subse quent doses of 0 35 gm (5 0 c c) are given on alternate days, provided no symptoms of toxicity other than nausea appear In the 17 days a total of 3 15 gm will have been given If a course of fuadin is ineffectual it is recommended that the patient receive tartar emetic Surgical treat ment may be necessary for complications such as urinary calculi, fistulae stricture and new growths

Incidence and Pre ention

Factors, which favor endemicity of schistosomiasis, vary greatly in different areas of Africa In Egypt schistosomiasis is characteristically a disease of those whose occupation or religion necessitates exposure to infected waters It is largely limited to peasants, land owners and Moslem priests who are exposed during ablutions and while engaged in agricultural pursuits and canalization work Infection in non residents invariably is acquired while hunting, swimming or bathing in infected waters

intestine and the rectum (Figs 5 6) The urinary bladder is rarely involved Lesions caused by eggs acting as foreign bodies in the intestine may consist of diffuse congestion infiltration sandy patches papillomata ulceration and erosion Papillomata occur most frequently in the descending colon sigmoid and rectum They are characteristically pedunculated and may occur as a single polypoid growth or as cauliflower-like tumors They are highly vascular friable and likely to bleed External tumors may develop about the anus or invade the sphincters Prolapse of the rectum frequently develops in advanced cases Persistence of the infection results in the thickening of all layers of the



Fig 6 Schistosomiasis mansoni An egg from a rectal polyp within a pseudotubercle with marked formation of fibrous tissue The embryo of the egg is replaced by tissue cells (after Hutchinson)

intestine which become hard and fibrous due to numerous eggs which fail to escape to the exterior and which become calcified in the tissues

Eggs laid in the large mesenteric veins and those which are unable to enter the intestinal wall are carried to the liver where they are trapped in the capillaries and cause a tissue reaction in the form of extravascular

during early colonial days and is now endemic in parts of Eastern and Northern Brazil Dutch Guiana, Venezuela and several islands of the West Indies including the Dominican Republic, Puerto Rico and Vieques French St Martin, St Kitts, Antigua, Guadeloupe, Martinique and St Lucia It is apparent that most snails in continental United States are either not susceptible to infection or they are not efficient hosts[3] The morphological characteristics and snail hosts of *S mansoni* are summarized in Table II

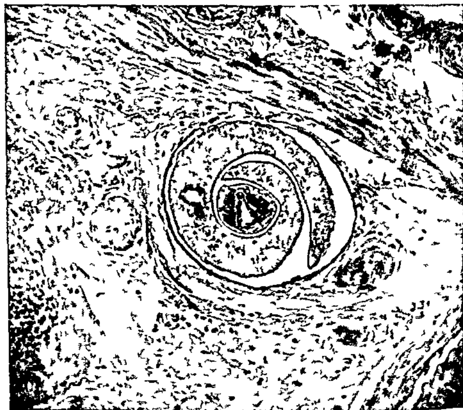


Fig 5 Schistosomiasis mansoni Cross section of a male and female worm in the veins at the base of a rectal polyp The male enfolds the female (after Hutchinson)

Pathology

The pathological changes occurring in schistosomiasis mansoni are similar to those of schistosomiasis haematobia except that the digestive tract as a whole, is characteristically affected, particularly the large

Prognosis

The prognosis in mild infections is good provided specific therapy is administered In severe and latent cases with extensive papillomata ulceration of the rectum and advanced cirrhotic changes in the liver the prognosis is poor

Diagnosis

The diagnosis of schistosomiasis mansoni is established upon demonstration of eggs of the parasite in fecal specimens or in biopsy material (Figs 4 B 7, 8) In stools presenting bloody mucus the direct fecal



Fig 7 *Schistosoma mansoni* Dead eggs obtained in biopsy material the commonest form encountered in rectal mucosa biopsies (photomicrograph after Hernandez Morales and Maldonado)

smear is a fast and efficient method of diagnosis but it has little value in the examination of most formed stools containing few eggs For the latter type of stool which is common in relapsed or chronic cases some method of concentration of the eggs is indicated Of these the gravitational sedimentation method originally described by Faust and Meleney in 1924[3] is the simplest and one of the best A large sample of stool or

infiltration and periportal cirrhosis In the early stages the liver is enlarged and smooth, but in advanced cases it is shrunken and presents the picture of advanced cirrhosis The result is obstruction of the blood flow through the liver and damming back in the portal vein, causing engorgement of the spleen, an important contributory factor in the development of splenomegalia According to Onsy[8] splenic enlargement in schistosomiasis is primarily due to response of the reticulo endothelial tissue of the spleen to deposition of eggs in it Eggs of the parasite also are carried to other sites including the lungs brain and subcutaneous tissue as in urinary schistosomiasis It is likely that most of these are transported by the vertebral venous system, described functionally in 1940 by Batson[11] Lung involvement may be caused also by eggs filtering through the capillary bed of the liver and by eggs from parent worms which occasionally may be present in the pulmonary arteries[12]

Clinical Course

The clinical course of intestinal schistosomiasis is essentially similar to that of urinary schistosomiasis Discomfort from itching and prickling sensation of the skin may occur for a few hours at the sites of penetration of the cercariae Otherwise the patient usually remains asymptomatic for at least from three to six weeks at which time eggs begin to pass with the feces Differences in the length of the incubation period are due to differences in the physical condition of the patient, the intensity of the first infection and the frequency and character of subsequent infection

According to Koppisch[13] the symptoms may have an abrupt onset with fever accompanied or not by a chill The fever which may run a remittent or intermittent course, may be accompanied by a generalized abdominal discomfort with occasional colic and by nausea, vomiting, diarrhea and cough which may be hacking and persistent An urticarial rash may develop which Girges[14] regards as an important physical sign Marked eosinophilia may occur at this time In the later stages cirrhosis with splenomegaly, ascites anemia and cachexia dominate the clinical picture The incidence of pulmonary schistosomiasis is high in Egypt but has been described less frequently elsewhere Meningitis and myelitis are rather rare complications Death in uncomplicated cases occurs usually from cirrhosis According to Koppisch[13] it is usually a matter of ten or more years before frank cirrhosis develops

tion is loosened by ringing with a clean applicator stick and the acid and ether layers are rapidly poured off and discarded The sediment then is agitated in the remaining fluid decanted onto a slide a coverslip is applied and it is examined microscopically for eggs of the parasite Weller and Dammin[1] reported marked increased efficiency in this method by the addition of 0 6 c c of 10 per cent aqueous triton NE to the acid feces mixture

In chronic or light infections repeated search may fail to reveal the presence of eggs in the feces In such cases rectal biopsy may be tried With this method as recommended by Ottolina and Atencio[16] and Hernandez-Morales and Maldonado[17], a rectoscope is introduced according to the usual technic the first rectal valve is visualized and feces if present are removed with a cotton swab From the edge of the fold a small piece of the rectal wall is pried loose with biopsy forceps and the site inspected for bleeding This rarely occurs but if present may be controlled by pressure with a piece of cotton The piece of tissue then is pressed between two glass slides with the help of Hoffman clamps and examined under the low power of the microscope The eggs if present are easily detected (Figs 7 8) Skin tests and serological reactions in their present stage of development cannot be regarded as of practical value in the diagnosis of schistosomiasis

Treatment

The treatment for intestinal schistosomes is the same as that outlined for urinary schistosomes

Prevention

The epidemiology of the intestinal schistosomiasis in Africa is similar to that of urinary schistosomiasis In Venezuela the endemic area is confined to the valleys in the central part of the northern coastal range coinciding with the geographical limits of the snail *Australorbis glabratus* which serves as the intermediate host There the disease is almost exclusively associated with irrigation of sugar cane[18] It is also associated with irrigation of sugar cane in southeast coastal Puerto Rico but elsewhere in Puerto Rico the infection is acquired usually while wading bathing fishing and laundering in infected streams and rivers

the entire specimen is emulsified in 10 to 20 volumes of tap water and strained through a wire mesh screen or cheese cloth into a tall glass container About an hour should be allowed to permit sedimentation, and the supernatant fluid then is siphoned away Further washing and sedimentation is carried on until the supernatant fluid is clear The supernatant fluid then is discarded and samples of the sediment examined under the microscope for eggs

The acid-ether method likewise is efficient and is particularly recommended when only a small amount of feces is available for examination With this method approximately one gram of fecal material is thoroughly emulsified in 5 c c of 40 per cent HCl (40 c c conc HCl



Fig 8 Schistosomiasis mansoni Large pseudotubercle with numerous dead eggs obtained in a rectal mucosa biopsy (photograph after Hernandez Morales and Maldonado)

diluted to 100 c c) in a small vial and then filtered through two layers of moist gauze stretched over a 5 mm funnel into a 15 c c centrifuge tube An equal amount of ether is added, the tube stoppered and shaken thoroughly It is then centrifuged for one minute at 1 500 R P M Upon removal from the centrifuge, the debris floating at the acid ether junc

the central nervous system have been reported more frequently in oriental schistosomiasis than in the other forms[19] There is no evidence of a predilection for the right or left hemisphere but most proven lesions have involved the parietal lobe Pulmonary complications apparently are not often encountered in *S japonicum* infection

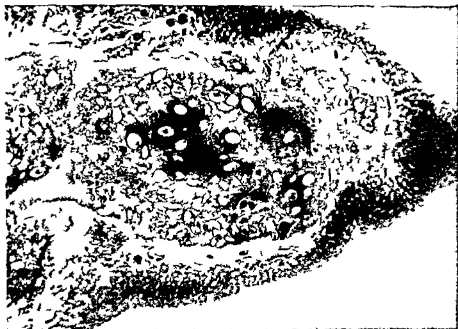


Fig 9 Schistosomiasis japonica Cellular response to eggs carried to the liver and cirrhosis

Clinical Manifestations

The clinical course of schistosomiasis japonica is similar to that of schistosomiasis mansoni Burning and itching of the skin may occur immediately after exposure to the cercariae From the third to the ninth week fever headache anorexia cough chills and malaise are frequent symptoms backache diarrhea and urticaria are seen less frequently There is generally a marked eosinophilia of about 15 to o per cent which may rapidly reach 50 to 90 per cent The total white blood cell

Schistosomiasis Japonica

Schistosomiasis japonica or oriental schistosomiasis is a chronic endemic disease of eastern Asiatic countries, produced by *Schistosoma japonicum*, Katsurada, 1904, characterized chiefly by abdominal and dysenteric symptoms, enlargement of the liver and spleen, ascites and terminal cirrhosis of the liver

Epidemiology

In China the disease is frequent in the valley of the Yangtze River from the eastern border of Szechwan to the mouth of this stream It occurs also in eastern Chekiang in eastern Fukien, in northern Kwangtung and in the Pingyang area of the provinces of Kwangsi and northern Hunan The disease is endemic also in western Yunnan It occurs frequently in the southern part of Formosa and probably exists in Korea The disease is prevalent throughout the southern part of Japan, especially in the prefecture of Hiroshima and the village of Katayama, where it is known as Katayama disease Oriental schistosomiasis is known to be endemic on five of the larger islands of the Philippines, Luzon Mindoro Leyte, Samar, the northern part of Mindanao and in the vicinity of Lake Lindoe in the Celebes (Dutch East Indies)

The adult worms show very little host specificity In addition to their occurrence in man, they are natural parasites of a wide range of different mammals in the endemic areas including the dog, cat, cattle water buffalo wild deer, horse, pig, goat, sheep and field rodents The biological characters of *S japonicum* and the names of snails which may serve as intermediate hosts are listed in Table II Its habitat in the human host is the same as that of *S mansoni* The urinary bladder, however is not involved Infection is almost invariably acquired by direct contact with cercariae in infected water Prenatal infection has been observed

Pathology

The lesions produced in schistosomiasis japonica are essentially the same as in schistosomiasis mansoni The outstanding features in chronic and long-standing infections are the great enlargement of the liver and spleen and rapid development of cirrhosis (Fig 9) Lesions involving

the venules of the liver There is no direct effect of the drugs on the egg Relapses are due to a gradual recovery of the ability of the female worms to lay eggs and their return to former locations in the mesenteric veins

Prevention

The control of schistosomiasis japonica is complicated by its widespread distribution in reservoir hosts the habitual use of human feces as crop fertilizers (China Japan the Philippines and Formosa) and the amphibious nature of the snail hosts which can withstand long periods of desiccation The disease is essentially an occupational one confined to those working in waters containing infective cercariae such as rice field farmers fishermen and boatmen Infection usually is due to wading bathing and laundering clothes in infected waters[3] About 1 000 cases of oriental schistosomiasis developed during World War II among American field forces The majority of these infections was acquired during bridge construction on Leyte Island Philippines[4]



Fig 10 *Schistosoma japonicum* Egg in feces The shell is characteristically hidden in adhering debris consisting of blood and tissue cells The rudimentary spine is apparent on the lower right border of the shell but is not well in focus (x 425)

Swimmer s Itch

Swimmer s itch also known as water itch and weed itch is a dermatitis characterized by papular eruption resulting from the penetration of the skin by non human schistosome cercariae The adult forms of these schistosomes are natural parasites in the abdominal veins of birds and lower mammals The cercariae are not host selective and they readily attack warm blooded animals which they may contact Upon

count may range from 12 000 to 50 000[6] Ascites and edema of the extremities anemia and diarrhea are pronounced symptoms in severe and prolonged infection

Neurological symptoms, including amnesia, aphasia, confusion diplopia disorientation epilepsy hemiplegia and personality changes, may appear within a few weeks after the primary invasion of the cercariae but usually are associated with a chronic and long standing infection They may occur in absence of previous evidence of schistosomiasis as determined by the patient's symptomatic history, physical examination and laboratory data[21]

Prognosis

The prognosis in oriental schistosomiasis is variable Mild and early cases usually respond favorably if treated In severe cases with cirrhosis or splenomegaly accompanied by ascites the prognosis is unfavorable, and improvement is slight, even with intensive treatment

Diagnosis

Intestinal infection with *Schistosoma japonicum* is diagnosed by the demonstration of eggs of the parasite in the stool or in biopsy material using the methods outlined for the diagnosis of schistosomiasis mansoni The egg usually is covered with fine fecal particles and is never as apparent and clear-cut in fresh material as the eggs of *S mansoni* and *S haematobium* (Figs 4 10) The diagnosis of cerebral schistosomiasis cannot be made with certainty without the aid of craniotomy Clinically the diagnosis is established with the aid of (1) history of exposure ( ) clinical manifestations (3) demonstration of the eggs in the stool specimen and (4) eosinophilia

Treatment

Oriental schistosomiasis should be treated with various antimony drugs as recommended for other schistosomes Experimental studies have shown that these drugs first produce a degeneration of the vitellaria or yolk glands and the ovary of the female worm, a degeneration of the testes of the male and shrinking of the whole worm Early in the course of treatment the worms tend to leave the mesenteric veins and move into

the venules of the liver There is no direct effect of the drugs on the egg Relapses are due to a gradual recovery of the ability of the female worms to lay eggs and their return to former locations in the mesenteric veins



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penetration of the skin of the abnormal host an inflammatory reaction results, and the cercariae are destroyed near the point of entrance (Fig 11) Following the destruction of the cercariae, the course of the lesion is one of recovery



Fig 11 Swimmer's itch forty eight hours after infection (photograph by Cort)

Symptoms

A prickling sensation may be felt a few minutes after emerging from infected waters Pin point macules may soon appear over the affected area The prickling sensation usually subsides, and no discomfort is experienced for a number of hours, when intense itching arises At this time the macules have developed into firm, discrete papules from ' to 5 mm in diameter The lesions usually fade within a week but some pigmentation may persist longer The clinical manifestations of swimmer's itch vary considerably in different individuals The first exposure probably is asymptomatic The speed of response is increased and the lesions are characteristically more severe and even incapacitating after repeated exposures Blondes are reported to be more susceptible than brunettes

Diagnosis

Swimmer's itch resembles the dermatitis caused by 'chiggers" or harvest mites (larval forms of various species of the genus *Trombidium*), and it might also be confused with that caused by poison ivy Chigger dermatitis is largely confined to areas of the skin covered by clothing i e the groin waistline legs and arm pits, whereas swimmer's itch appears on exposed parts of the body It differs from ivy poisoning in that the irritation is confined to the immediate spots where the cercariae enter the skin The lesions in swimmer's itch do not spread and

usually do not show watery blisters as is common in poison ivy dermatitis The cercariae may be antigenic[8, 27], an important factor to be considered in diagnosis of human schistosomiasis by skin tests and serological reactions

Prognosis and Treatment

The prognosis is excellent and the condition subsides without serious consequences No specific treatment is known These cercariae like other schistosomes penetrate when the water dries on the skin Brisk rubbing of the exposed parts of the body with a towel before the water dries will remove most of the cercariae from the skin A rub down immediately upon leaving the water has proved to be a wise preventive measure

Incidence

Swimmer's itch has been reported from various countries throughout the world including both temperate and tropical zones In North America it is particularly prevalent in the northern midwestern states and the central provinces of Canada (Great Lakes region) where it constitutes a definite bathing beach problem Swimmer's itch usually appears about the middle of July and is at its worst during spells of warm weather in July and August in this region Four different species of dermatitis producing schistosome cercariae are known from the Great Lakes area Of these *Cercaria stagnicolae* is the most important since its snail host, *Stagnicola emarginata,* is the commonest beach snail[28] The natural host of the parent worms of this cercaria is not known

Prevention

Satisfactory methods of control of schistosome dermatitis have not been developed as yet Where a bathing beach is cut off to a considerable extent from the rest of the lake the snails can be killed by hand sowing pea coal size copper sulphate crystals over the snail beds This method is not effective on open beaches since the areas to be covered

are usually too large, and it is further objectionable because the chemical is lethal to other aquatic animals, including fish

DISEASES DUE TO INTESTINAL, LUNG AND LIVER FLUKES

Fasciolopsiasis

Fasciolopsiasis is an infection of the small intestine with *Fasciolopsis buski* (Lankester 1857), Odhner, 1902, in which clinical manifestations may be either present or absent Endemic fasciolopsiasis is distinctly oriental in distribution It is particularly prevalent in Chekiang Province China where it is one of the principal causes of an illness affecting the community health in general

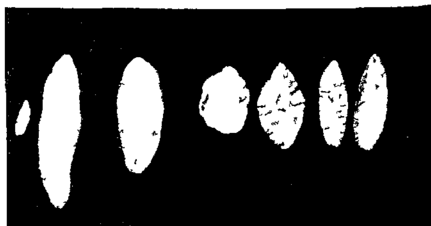


Fig 12 *Fasciolopsis buski* Adult flukes from man natural size (after Goddard)

Epidemiology

Fasciolopsis buski is the largest trematode of man, measuring up to 70 mm in length and to o mm in breadth The body is fleshy opaque and has a spiny cuticle The ventral sucker is prominent and lies close to the inconspicuous oral sucker (Fig 12) The eggs are large averaging 183μ in length by 83μ in breadth They are light brown in color, possess

a very delicate operculum and show no development when found in freshly passed feces (Fig 13) They require from two to four weeks in water before the miracidia begin to hatch These miracidia penetrate snails of the genera *Segmentina* and *Hippeutis*, in which they develop into sporocysts

The sporocysts give rise to two generations of rediae and finally a generation of cercariae The latter, after leaving the body of the snail, swim about for a short time but become encysted as soon as a favorable spot is found usually on the plant on which the snail is feeding Root vegetables particularly the water caltrop *Trapa natans*, and the water chestnut *Eliocharis tuberosa*, frequently bear great numbers of the encysted cercariae

In the Chekiang Province, particularly in a large area just south of Hangchow these root vegetables are grown as crops in shallow water and fertilized with freshly collected night soil They are brought into local markets from the middle of July to the end of September for sale as fresh tubers After September they are dried and sold as such until the next spring

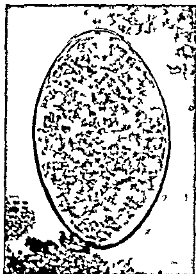


Fig 13 *Fasciolopsis buski* Egg in feces The position of the delicate operculum is indicated by the two lateral interruptions at the anterior tip of the shell (x 4 5)

As drying quickly kills the metacercariae it is only the fresh nuts that are of any danger The danger of infection in the market is greatly enhanced because the vendor constantly sprinkles the caltrops with a brush dipped into unboiled canal water Most of the caltrops are eaten raw at the time of purchasing while those eaten in the fields are taken directly from the water They are peeled with the teeth during which process the outer cyst wall becomes ruptured and the cyst is deposited into the mouth and passes on to the duodenum Here the inner cyst wall is dissolved away and the immature worm attaches itself to the mucosa of the upper intestine and rapidly grows into the adult stage[3]

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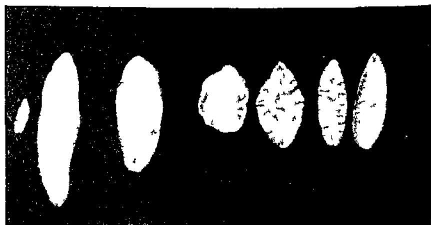


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HETEROPHYIDIASIS

Heterophyidiasis is an infection of the small intestine with trematodes of the family *Heterophyidae*, of which *Heterophyes heterophyes* (v Siebold 185) Stiles and Hassall 1900, is the commonest species in feeding man This species is also a common parasite of dogs and cats and is reported also for the fox It is prevalent in Egypt Palestine and the Far East including Japan southern Korea Formosa and the Philippine Islands *H heterophyes* is the smallest trematode of man measuring about 2 mm in length and 0 4 mm in breadth It is of the distome type and in addition to the oral and an anterior median ventral sucker bears a third conspicuous sucker which surrounds the genital pore The egg has a relatively thick brown shell about 30 μ by 17 μ, and contains a fully developed miracidium when deposited

The eggs hatch after ingestion by appropriate snail hosts *Pirenella conica* in Egypt and *Cerithidea cingulata microptera* in Japan and China The cercariae upon leaving the snail host penetrate and encyst in the mullet *Mugil cephalus* or other fresh water fish Inasmuch as the encysted metacercariae are able to survive seven days in brine both raw and salted fish are sources of infection This parasite appears to be harmless to the host

The *diagnosis* is made upon the demonstration of the eggs in the feces They may be confused with the eggs of the liver fluke *(Clonorchis sinensis)* and *Metagonimus yokogawai* another heterophyid trematode and a common intestinal parasite of man fish eating mammals and birds *M yokogawai* is prevalent in the Far East including Japan China Formosa and Dutch East Indies and also occurs in the maritime provinces of the Union of Socialist Soviet Russia the Balkans and has been reported from Spain Specific diagnosis is best determined upon adult worms obtained from anthelmintic treatment For *treatment* tetrachlorethylene is prescribed for hookworm infection (see Chapt XXXVIII, Vol V of Oxford Medicine) is recommended

Some heterophyid trematodes which are normally parasitic in lower vertebrates (fish eating mammals and birds) have been reported from man in the Philippine Islands Japan and Formosa The infections are contracted solely by eating raw or semi raw fish harboring the encysted cercariae Apparently because of an unbalanced parasitic relationship these worms in the human host burrow into the deeper tissues of the intestinal wall where they erode the tunica propria but provoke only a mild or no inflammatory reaction As a consequence they are not walled

Pathology

Foci of inflammation may occur at the point of attachment of the parasites. The lesion may involve the capillaries of the wall of the intestine, causing hemorrhage, ulceration and infiltration of the mucosa with polymorphonuclear leucocytes, eosinophils and lymphocytes. When occurring in large numbers, the parasites may cause abdominal discomfort, nausea, tenderness below the right costal margin, diarrhea, anemia, anasarca and fatal cachexia. Large numbers are not always necessary to give rise to noticeable symptoms, for many patients harboring but a very few worms may be affected.[29] Leucocytosis with a relatively high eosinophilia is typical.[30]

Diagnosis and Treatment

The diagnosis usually is made on the finding of the eggs in the stool. The simple smear method is sufficient to reveal these eggs when present, even in light infections. In case of uncertainty as to the identity of the egg, search should be made for adult trematodes in stools passed immediately following anthelmintic treatment, upon which form a specific diagnosis may be established. Natural infections with *F. buski* in persons other than native residents of endemic areas appear to be exceedingly rare. Hexylresorcinol crystoids (caprokol), administered as for ascariasis (see Chapt. XXXVIII, Vol. V of Oxford Medicine), has been reported highly effective in removing the parasites from the intestine.[31] Tetrachlorethylene is probably equally efficacious.

Prevention

The control of fasciolopsiasis is exceedingly difficult. In Chekiang water caltrop and chestnuts are very important crops. They are produced on time-honored customs apparently impossible to change and which particularly favor endemicity. Snail control is neither feasible nor advisable. A long patient educational program against the custom of peeling the raw caltrop nuts with the teeth promises the best results in the final analysis.

maturity the cercariae leave this host to enter and encyst in other snails and mussels The mussel *Corbicula lindoensis*, constitutes the important source of animal protein for the people and is believed to be the main source of human infection Similarly the encysted cercariae of *E revolutum* are transmitted to man by the mussel *Corbicula producta*

AMPHISTOMIASIS

Amphistomiasis is a general term applied to infection with trematodes of the family *Paramphistomatidae* Amphistomes are natural parasites in the rumen of cattle sheep goats deer and the small intestine of swine beaver musk rat and voles They rarely infect man Only one species *Gastrodiscoides hominis* appears to be a characteristic human parasite It inhabits the cecum and large intestine This parasite has been reported frequently from Assam and it is also endemic in Cochin China and the Malay States In the living condition it is reddish in color and may be readily recognized by the conical body with a conspicuous ventral sucker at the posterior portion The eggs are large averaging 150 µ x 60 µ and are passed with the feces The life cycle is unknown but cercariae of related species are known to encyst on vegetation Gastrointestinal symptoms particularly diarrhea have been attributed to the presence of this species

Thymol has been used successfully in expelling amphistomes from the intestine but tetrachlorethylene probably is the drug of choice The pig is an important reservoir host

PARAGONIMIASIS

Paragonimiasis is an infection by *Paragonimus westermani* (Kerbert 1878) Braun 1899 commonly known as the lung fluke of man The disease is characterized by cough and bloody sputum In addition to man lung flukes have been described from many lower mammals including the dog cat fox mink tiger leopard mongoose swine opossum muskrat and rats With the exception of *P iloktsuenensis* Chen 1940 in brown and black rats of Canton China the specific identity of these non human lung flukes still is questioned The weight of evidence however favors the view that they and the human lung fluke are of one and the same species *P westermani*

off by fibrosis and their eggs are carried by the lymphatic system into the blood stream and are distributed to different organs where they may cause inflammation and serious injury In Manila, Africa and his co workers[3] have observed them with marked frequency in the myocardium and the mitral valves of persons dying of cardiac failure Since hyper ophyid flukes of lower vertebrates are world wide in distribution, it is very likely that the condition in man, as observed by Africa, is not peculiar to the Philippine Islands

Echinostomiasis

Echinostomiasis is a general term applied to any infection with trematodes of the family *Echinostomatidae* There is no characteristic symptomatology Echinostomes are world-wide in distribution and for the most part, are intestinal parasites of birds carnivores and swine A few species have been reported from man These generally are regarded as incidental infections The pathology and symptomatology of echinostome infection in man have not been adequately studied Echinostome infection may be detected by finding the eggs in the feces but specific diagnosis must be made on adult worms obtained from anthelmintic treatment The type is readily recognized by the fleshy anterior head collar bearing a single or double row of stout spines

Echinostoma revolutum is a cosmopolitan parasite of the cecum and rectum of domestic and wild fowl It is reported to be relatively common in man in Formosa *E lindoensis* has been reported recently as a common parasite at Lake Lindoe Central Celebes, but no natural reservoir host is known[3, 34] *Euparyphium ilocanum*, also known as *Echinostoma ilocanum*, has long been known to occur as a human parasite in the Island of Luzon, Philippines It occurs there also in the rat and dog

Echinostome cercariae characteristically encyst within the tissues of the snail in which the rediae develop or they may leave this host and later reenter it or almost any available snail in order to encyst Infection of the definitive host follows ingestion of infected snails Human infection with *E ilocanum* in man results from eating *Pila luzonica*, a snail which is regarded as a delicacy and which is eaten straight from the shell or with a sprinkling of salt or a little vinegar or lemon juice insufficient to injure the encysted metacercariae The cercariae of *E lindoensis* develop in a small planorbid snail *Anisus (Gyraulus) sarasinorum* Upon

maturity the cercariae leave this host to enter and encyst in other snails and mussels The mussel *Corbicula lindoensis*, constitutes the important source of animal protein for the people and is believed to be the main source of human infection Similarly the encysted cercariae of *E re o-lutum* are transmitted to man by the mussel *Corbicula producta*

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Incidence

Paragonimus westermani has a wide geographic distribution Impo tant endemic foci of human infection are, however, confined to t Orient, namely, mountainous districts of Japan, Korea, Formosa, Ch liang Province, China and the Philippine Islands Less importa endemic areas of infection in the Orient include French Indo Chin Siam Malay States, Assam India Java, Sumatra and Samoa Enden foci also occur in South America, and a few sporadic infections ha been reported from Africa

In the United States *P westermani* appears to be a fairly comm parasite of the cat, dog mink, swine muskrat and opossum in and e of the Mississippi River valley an area which closely parallels t geographic range of its only known North American snail host *Poma opsis lapidaria* A single human infection, which may have been acquir within this area was reported in 1910[3] No other reports regardi indigenous infections in man in the United States or Canada have be made since that date

Endemic foci of human paragonimiasis occur only in countries parts of certain countries, where the people commonly eat raw salt or pickled fresh-water crayfish and crabs in which the infective ce cariae have encysted Because of the world wide distribution of t parasite in reservoir and intermediate hosts sporadic cases of hum infection can be expected to appear almost anywhere should raw fres water crayfish and crabs be eaten either as an adventure or because necessity A few cases of paragonimiasis developed during World W II among members of the United States Naval and Marine Corps st tioned in Samoa Solomon Islands[6], an area without previous recor

Epidemiology

Adult worms when killed and preserved have an oval or elliptic form resembling a coffee bean both in size and shape They are of reddish brown to a slate color when first removed from the body b soon become grayish on exposure The cuticle is spinous The or sucker is situated at the anterior extremity of the body and ope anteriorly in well extended specimens In contracted specimens t mouth is ventral The suckers usually are of about equal size slight

less than 1 mm in diameter The ventral sucker is situated somewhat anteriorly to the middle of the body and often lies completely invaginated leaving a relatively narrow external opening visible from the body surface The genital pore lies on the mid ventral surface close to the posterior margin of the acetabulum The excretory bladder is very large in all its growth phases and its central position and size are clearly indicated in cross sections of the parasite (Figs 15 18)

The eggs of *Paragonimus westermani* are oval yellowish in color and have a relatively thick shell They vary considerably in size, even when obtained from a single host measuring from 85 μ to 100 μ in length by 50 μ to 67 μ in breadth They show no development when they leave the host the fertilized cell in the single cell stage surrounded by several yolk globules (Fig 14) The eggs of *Paragonimus westermani* usually escape from the human host in the sputum but if the host swallows his sputum they may also be found in the feces The development of the miracidium is slow and may require from four to six weeks before it escapes from the shell Under optimum conditions hatching takes place in about sixteen days

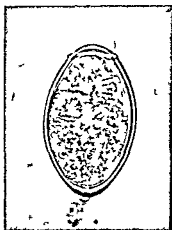


Fig 14 *Paragonimus westermani* Egg discharged in sputum (x 425)

At least six species of fresh water snails of the family *Thiaridae* (generally referred to as *Melania* in medical literature) may serve as the first intermediate host of *Paragonimus westermani* in the Orient Of these *Semisulcospira libertina* in Japan and *Hua (Hua) ningensis* in China and Korea are perhaps the most important species in the propagation of the parasite in the Orient *Pomatiopsis lapidaria* is the only snail host known in North America

The cercariae after their escape from the snail penetrate into the body of several species of fresh water crustacea of the genera *Potamon Sesarma*, *Eriocheir Astacus* and *Cambarus* and encyst in the liver muscles and in the gills

While it is possible that some infections are acquired from drinking water containing living cysts which have been freed from crabs it is highly probable that most infections are incurred by a direct ingestion

of the cysts from crustaceans serving as second intermediate hosts either in connection with the handling of crabs while preparing them for food or more especially by eating them raw or imperfectly cooked

After the entrance of the encysted larvae within the body of the final host they show a remarkable tendency to migrate and invade tissues other than the lungs until they are sexually mature After being swal



Fig 15 Paragonimiasis Showing penetration of the wall of the jejunum by a young fluke The several circular structures within the parasite are cross sections of its intestinal cecae The clearly defined central area represents the excretory vesicle Experimental infection (original photomicrograph of material received from Dr S Yokogawa)

lowed with the flesh of the crab the young parasites escape from their cysts in the small intestine of the host Within several hours they penetrate through the intestinal wall and reach the abdominal cavity (Fig 15) They then make their way along the peritoneal cavity and penetrate the diaphragm (Fig 16) They may live for some time in the peritoneal cavity and penetrate other organs before reaching the diaphragm Therefore at the time of piercing the diaphragm they may be in an early stage of development or at any stage up to sexual maturity

Before entering the thoracic cavity they may burrow into various tissues and organs such as the liver spleen omentum and mesenteries Most frequently they penetrate the liver but enter it for a short distance only and then turn and escape thus making characteristic blind passages (Fig 17) Approximately twenty days after infection most of the worms from a given infection will have entered the chest cavity and penetrated the lungs Not all the worms which enter the abdominal cavity will migrate into the diaphragm Accordingly in heavy infections some worms may remain in the abdominal cavity and there reach maturity within fibrous cysts Such a cyst may attain considerable size and contain a large number of living flukes

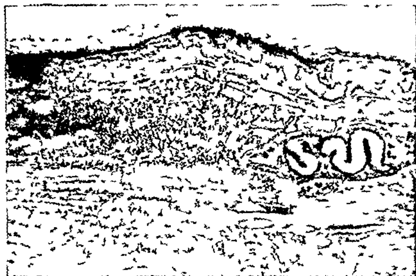


Fig 16 Paragonimiasis Showing penetration of the diaphragm by a young fluke its path of migration (characteristically with the long axes of the muscle fibers) and cicatrization of the diaphragm Experimental infection (original photomicrograph of material received from Dr S Yokogawa)

Some of the worms may migrate to the brain but apparently they do not remain in this tissue for their development The course to the cranial cavity is believed to be along the soft tissues of the neck and through the large foramina especially the jugular foramen since in

human cases the pathological changes in the brain are almost always in the temporal or occipital lobes near the jugular foramen

The adult flukes ordinarily occur in the lungs of the final host They lie within fibrous cysts commonly of a size sufficient to admit the tip of the finger The cyst usually communicates with a bronchiole, thus permitting the escape of the eggs in the sputum Although cysts of ordinary size commonly contain a pair of flukes, cysts containing a single worm frequently occur In heavy infections the cysts may coalesce

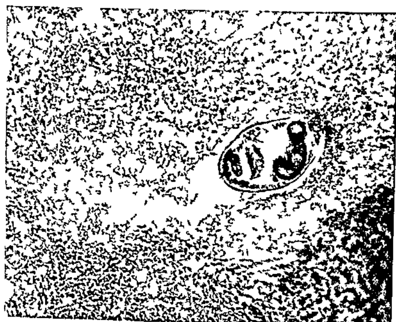


Fig 17 Paragonimiasis Showing young fluke in the liver its path of migration tissue destruction and cellular response Experimental infection (original photomicrograph of material received from Dr S Yokogawa)

The cysts represent dilatations of the smaller bronchi or bronchioles and their walls are composed of connective tissue with a lining of stratified squamous epithelium arising through metaplasia of the columnar or cuboidal bronchial epithelium The cyst wall may show cellular infiltration with numerous eosinophiles and often giant cells (Figs 18 and 19) Cysts may undergo caseation, and abscesses occur frequently Associated with these lesions there may be extensive fibrotic changes bronchiectasis and emphysema Eggs which fail to leave the bronchi,

may become lodged in any portion of the lung and as foreign bodies incite the formation of small pseudotubercles

Clinical Course

The onset of the disease is insidious and there then follows gradually increasing symptoms referable either to the chest the abdomen or the lymphatic system

Patients suffering from pulmonary paragonimiasis may have a chronic cough which usually is most pronounced in the morning upon rising Considerable blood stained or viscid sputum is ejected in which

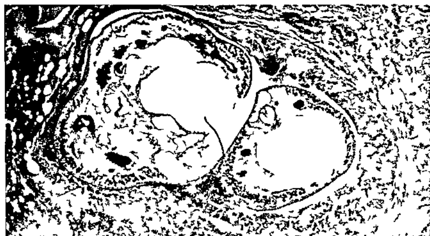


Fig 18 Paragonimiasis Pulmonary cyst showing encapsulation of two parasites lying in a purulent exudate The adjacent tissue shows atelectasis and pneumonic areas The section of the parasite to the right shows the oral sucker pharynx the large excretory vesicle and the strongly developed vitellaria throughout the periphery beneath the cuticle (original photomicrograph of material received from Dr S Yokogawa)

the ova of the parasites may be found by microscopical examination The hemoptysis usually is slight in degree but in some instances may be severe There may be vague discomfort in the chest but most patients cannot ascribe a definite pain to a definite location The breath sounds usually are normal and rales usually are not present If the infection is abdominal there may be spasm of the abdominal wall When

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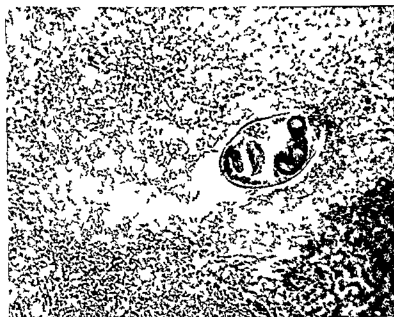


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Diagnosis

The diagnosis of paragonimiasis is established by the finding of ova in the sputum feces or in fluids obtained by aspiration It is often necessary to repeat this examination on different days before excluding the possibility of paragonimiasis Other laboratory tests are essentially negative The geographical distribution and prevalence of the disease and the travel and food habits of the patient must be taken into account also in making the diagnosis

Treatment

Thus far no satisfactory treatment is known for paragonimiasis Emetine is the drug most used at present Hemert in Ecuador reported cures in eighty per cent of his patients who had received treatment with emetine Yokogawa and associates[4] reported encouraging results with prontosil in combination with emetine given intravenously This method of treatment by Yokogawa frequently referred to in the literature appears to be fraught with danger Much further study and confirmation is required before it can be recommended Surgery has been recommended in cases which do not respond to chemotherapy

Prevention

Total abstinence from uncooked fresh water crayfish and crabs in the diet of any country is at present the only reliable measure against paragonimiasis

CLONORCHIASIS

Clonorchiasis is an infection of the bile ducts with *Clonorchis sinensis* (Cobbold 1875) Looss 1907 the Asiatic liver fluke of man The disease is characterized by fibrotic changes in the liver

Epidemiology

Clonorchis sinensis is not only a parasite of man but also is frequently found in fish eating mammals of the Orient It is common in the coun

other tissues and organs are involved, appendicitis, enlargement of the prostate, epididymitis, cirrhosis of the liver and diarrhea from intestinal ulceration may result Paragonimiasis may occur also in a generalized form associated with fever, enlargement of the lymph nodes and cutaneous ulcerations The blood may show a moderate degree of leucocytosis, but there is usually an essentially normal differential count Cerebral involvement frequently is associated with a form of Jacksonian epilepsy and may result in paralysis, visual disturbance or aphasia

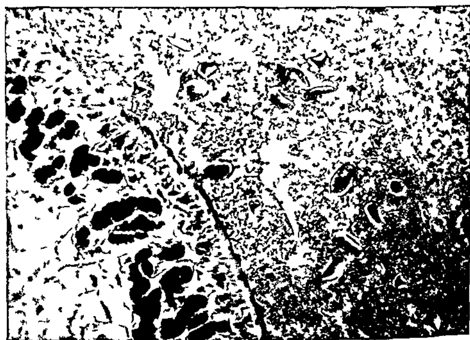


Fig 19 Pulmonary paragonimiasis Eggs in the cavity fluid and a section of an *adult fluke showing its spinous cuticle vitellaria and body parenchyma* (site selected from Fig 17 x 85)

Prognosis

The prognosis is largely dependent on the degree of infection Patients with light infections rarely become seriously ill In the case of heavy infections or in those cases in which serious complications have developed the prognosis is bad

is located at the narrower pole and is vaulted and so inserted within the rim of the shell that its contour usually does not follow that of the main part of the shell The shoulders at the opercular rim often are prominent and constitute a diagnostic character (Fig 20)

The eggs of *C sinensis* are deposited by the adult worms in the biliary passages of the host and from there they pass to the intestinal tract At present the exact method by which the snail host becomes infected with *Clonorchis* is not definitely known Experimental evidence however indicates that the miracidia do not hatch in the open and actively penetrate the snail host Apparently the unhatched ova are taken passively with food into the snail s digestive tract and after hatching the miracidia penetrate the vascular spaces for development into cercariae Species of the subfamily *Bulinimae* are the only known snail hosts (1) *Parafossarulus manchouricus* the main first intermediate host in Japan and of secondary importance in China and (2) *Bulimus fuchsianus*, the most important species in southern China The cercariae upon leaving their snail host attach themselves to the body of fish and after shallow penetration of the tissues, encyst in the musculature on the underside of the scales or on the skin



Fig 20 *Clonorchis sinensis* Egg in feces (x 425)

More than thirty species of fresh water fishes are known to harbor the cysts of *Clonorchis sinensis* Of these *Pseudorasbora parva* is most commonly involved It has a wide distribution and is often eaten raw, in vinegar or in soy sauce

The chief source of infection is by the direct ingestion of fish containing the cysts when served raw or only partially cooked Upon ingestion of the cysts by the final host the encysted larvae are liberated in the duodenum and they then migrate directly into the bile ducts where they grow to maturity By the sixteenth day after ingestion of the cysts some of the worms may be sexually mature and producing ova Usually the majority do not reach sexual maturity until after the twentieth day

tries adjacent to the China and Yellow seas namely, Japan, Korea, China, Formosa and French Indochina. The infection appears to be limited to the geographic distribution of the first intermediate hosts, bulimoid snails. In man it has been reported frequently from countries outside of the Orient including the United States, but in all such cases the infection has been among persons who originally came from or who had lived in endemic districts of China or Japan. The incidence of infection in this group may be high. There is no authentic record of the spread of this parasite into new regions by immigration.

Clonorchiasis is rather generally distributed throughout Japan, but the heaviest focus of infection is in the Okayama district. In Korea the infection occurs in the southern part of the peninsula. In China the most important focus of human infection is in the Kwantung Province, southeastern China. Occasionally indigenous infections in man are encountered in Central China but in North China, where fish is customarily cooked, it is confined to animals. The most heavily infected area of French Indo China is found in the delta of the Red River.

The incidence of *Clonorchis sinensis* in cats and dogs is high throughout endemic centers of China. Chen[39] found about 44 per cent of the dogs and about 80 per cent of the cats of the Canton area and about 59 per cent of the cats of the Foochow area infected.

Clonorchis sinensis normally inhabits the bile passages of its mammalian host. It migrates to the more distal portions of the bile tracts when still immature and there grows to maturity. Apparently there is little or no migration from this position during its adult life. The worms usually are found free in the cavity of the ducts or crowded into small bile capillaries. One lobe of the liver sometimes may be heavily infected (the left lobe) while the remainder of the organ will be relatively free from the infection. They frequently invade the pancreas.

Adult specimens of *Clonorchis sinensis*, when alive are opalescent gray but if allowed to die in situ preceding autopsy, they become discolored through the absorption of the bile pigment and take on a deep brown color. Due to a weakly-developed musculature it is quite transparent and shows the internal organs in shadowy relief. The body has a more or less rounded tapering posterior end and measures about 15 mm in length by 3 mm in breadth.

The normal egg has a yellowish brown color, is oval in shape, resembling an old fashioned carbon filament electric light bulb and has an average size of 9 μ in length and 17 μ in breadth. The embryo is fully developed at the time the ova are passed from the host. The operculum

Pathology

During early invasion the liver may be somewhat enlarged but later there may be more or less extensive fibrosis Local dilatations of the bile ducts are sometimes found containing large numbers of the flukes These appear as whitish cysts on the surface of the liver and on section numerous cavities are found throughout its substance Microscopically the cysts show marked fibrotic changes in their walls and varying degrees of cellular infiltration in which eosinophiles often predominate There may be loss of biliary epithelium due to the injury brought about by the presence of the flukes but usually a succession of minor injuries leads to hyperplasia of the biliary epithelium the proliferation of which leads to the production of adenomatous changes (Fig 21) The proliferation usually is confined to the cyst itself, but because of the higher incidence of primary carcinoma of the liver where clonorchiasis is endemic, it is believed that the parasite may play an important role in the development of this malignancy While the pathological effect of flukes is localized for the most part, certain cases show evidence of constitutional changes possibly brought about by the absorption of metabolic products of the parasites True diffuse cirrhosis is not produced and ulcerative lesions are rare Local eosinophilia may be marked

Symptomatology

The disease as usually seen is a predominately chronic one occurring in Chinese especially Cantonese Symptoms are vague and indefinite but frequently include abdominal fullness and pain diarrhea and hepatic disorders Severe consequences such as chronic proliferative cholangitis cholecystitis and portal cirrhosis have been observed Eosinophilia may be present but otherwise there is no significant change in the blood picture Acute symptoms have not been described in Chinese or Japanese patients

According to Koenigstein who studied an outbreak of clonorchiasis during World War II in a community of displaced persons of European origin accumulated in Shanghai the clinical picture is that of an acute infection and starts with general malaise and subfebrile or febrile temperature The sclerae and skin frequently show an icteric tint The liver may be enlarged and tender and usually there is marked tenderness in the right ninth or tenth intercostal space in the back There is a slight

A small number of flukes in the liver of the host usually give rise to minimal pathological changes and probably the majority of individuals harboring these parasites fall into this category and might be classified as carriers When large numbers occur, however, they produce definite injury to the host



Fig 21 Clonorchiasis Adenomatoid hyperplasia of the biliary epithelium Cross sections of several flukes are present in this dilated bile duct

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respectively The pathologic changes are quite similar to those described for C *sinensis*

Opisthorchis felineus is a common parasite of carnivores in central European countries and Russia It apparently occurs quite frequently in East Prussia and the Ob Basin as a human parasite Infection in the mammalian host results from eating raw or inadequately cooked fresh water fish containing encysted cercariae The diagnosis is established upon finding the characteristic eggs in the stool The eggs are similar to those of *C sinensis* and various heterophyid species The endemic areas of O *felineus* and C *sinensis* do not overlap

Fasciola hepatica is the common liver fluke of domestic sheep and cattle It is cosmopolitan in distribution and is prevalent in cattle and sheep raising countries wherever susceptible snail hosts are present Human infection is not common but cases have been reported from every continent None is known for the United States and Canada but the infection has been reported from Central America and in Cuba human fascioliasis is recognized as a problem of major importance

The life cycle of *Fasciola hepatica* closely parallels that of the large intestinal fluke of man *Fasciolopsis buski* The miracidium hatches from the egg about three weeks after oviposition and finds its way into fresh water snails especially species of the genera *Galba Lymnaea* and *Fossaria*, in which the cercariae develop The cercariae upon their escape from the snail host swim to the surface of the water and there encyst the encysted forms then float freely on the surface film of water The cercariae may attach themselves also to submerged grasses or aquatic vegetation for encystment Watercress is probably a common source for infection in man When these cysts are swallowed by a suitable mammalian host the young flukes escape from their cyst wall in the small intestine pass through the intestine into the body cavity and enter the liver from its surface They may wander about in the liver a month or more before settling down in the bile ducts where they mature Young specimens also may migrate through the body tissues, or they may be carried in the blood stream to locations other than the liver Parasites have been observed in the lungs brain veins and in subcutaneous tissue

Fascioliasis in man characteristically runs a long chronic course accompanied by symptoms related to the liver gall bladder intestinal tract and nervous system The blood may show marked eosinophilia which may be due in part to concomitant helminthiases or to other factors Aberrant flukes in the connective tissue give rise to painful

leucocytosis and an eosinophilia ranging, on an average, from 10 to 40 per cent In the absence of re-infection, the acute symptoms subside after a few weeks, but malaise remains in most cases

The *prognosis* in light infections is good, but is poor in heavy, long standing cases

Diagnosis

Clonorchiasis should be considered in the differential diagnosis of patients who present suggestive symptoms and have emigrated from or have lived within endemic areas in the Orient An absolute diagnosis usually is made on the finding of the egg in the stool or in material obtained from duodenal intubation

Treatment and Prevention

No satisfactory treatment has been discovered for clonorchiasis Gentian violet medicinal is clonorchicidal and appears to be of some value[12] The dosage of the drug is the same as that recommended for enterobiasis (see Chapt XXXVIII in this volume)

Throughout the endemic regions of the Orient clonorchiasis occurs only in persons who eat raw fresh-water fish In the Kwangtung Province particularly in the Canton area which is the chief endemic center in China, conditions are particularly favorable for infection Fresh water fish culture is a very important industry in the delta region[13] An important source of food for the fish is human excreta discharged into the rearing ponds from latrines erected over the water The ponds are also natural habitats for the essential snail host Thorough cooking of fresh water fish is the only effective means of preventing clonorchiasis

OPISTHORCHIASIS AND FASCIOLIASIS

In addition to *Clonorchis sinensis*, a few other species of liver flukes, which are natural parasites of lower mammals, are incidental parasites of man Of these *Opisthorchis felineus* (Rivolta, 1884) Blanchard, 1895 and *Fasciola hepatica* Linn 1758 are important pathogens Infections with these two species are known as opisthorchiasis and fascioliasis,

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nodules Recently Neghme and Ossandon[44] reported a case in which a single fluke was found in a hard inflammatory nodule , cm in diameter, located over the right eighth rib The tumor was adherent to the skin The patient also had eggs of *F hepatica* in the stool

Hepatic fascioliasis is diagnosed upon the finding of the eggs of the parasite either in the stool or in bile obtained from duodenal intubation The prognosis usually is good or fair in mild infections, grave in heavy infections Emetine hydrochloride given in small doses has been found to be of definite value in the treatment of hepatic fascioliasis[45]

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CHAPTER XXXVIII

DISEASES DUE TO NEMATODES OR ROUND WORMS

By DONALD L. AUGUSTINE

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in length Nematodes usually are white or of a light pink color but some parasitic species may be blood red due to ingested blood of the host The body is covered by a hardened, non cellular, glistening layer the cuticle which is characteristically marked by regularly arranged transverse markings or striations often exceedingly fine These striations are superficial and involve only the cuticle there is no true segmentation In some species the cuticle is longitudinally thickened forming lateral sharp edged expansions termed *alae* These *alae* may extend the entire length of the body or may be confined either to the anterior or posterior portions of the body

The body wall is composed of a hypodermis which is situated beneath the cuticle and a single layer of longitudinal muscles The hypodermis is essentially a delicate protoplasmic tube in which distinct cell walls may be present but usually it is syncytial It is internally thickened in four longitudinal lines the dorsal ventral and lateral chords which extend the entire length of the body thus dividing the latter into quadrants The lateral chords are more prominent than the dorsal and ventral chords Attached to the hypodermis is a single layer of longitudinal muscles separated by the longitudinal chords of the hypodermis into four primary muscle fields The muscle cells are peculiar in that only a portion of the protoplasm is differentiated into contractile fibers The rounded undifferentiated portion including the nucleus projects inwardly

The vital organs are suspended in the body cavity which lacking epithelium is lined by a delicate connective tissue layer of mesenchymatous origin The digestive tract consists of a straight tube connecting the extremities of the worm The mouth is terminal at the anterior end of the body and it may be surrounded by lips bearing sensory organs The mouth is followed by a buccal cavity an esophagus intestine and a rectum terminating in a ventral terminal or subterminal anus or cloacal opening The buccal cavity may be large or indistinguishable and in some species it is supplied with teeth or rasps The esophagus is a muscular structure with a triradiate lumen It frequently terminates in a more or less conspicuous bulb or valvular apparatus The intestine is composed of a single layer of epithelial cells which are covered by irregular muscle fibers and a connective tissue sheath The rectum is lined with cuticle as is the buccal cavity and the esophagus In the male worm various developments of the dorsal wall of the cloaca give rise to accessory sexual structures such as spicules and the gubernaculum

Introduction

Invertebrate animals variously known as roundworms, threadworms, nematodes and nemas belong to the phylum, *Nemathelminthes*, and to the class *Nematoda*. This group of animals is exceedingly large and includes many thousands of free-living and parasitic species. Free living nematodes abound in almost every conceivable environment. Some are herbivores, some are carnivores and others are efficient scavengers. Most free-living nematodes are seen rarely because of their minute size.

Nematodes are known most widely as parasites. Many species are parasites of plants, causing great economic loss in agricultural and horticultural industries. Hundreds of species are parasites of animals, frequently causing serious disease of vertebrates, particularly of domestic animals and man. Morphologically the parasitic species are strikingly similar to the free-living forms.

Nematodes have elongated cylindrical bodies tapering slightly toward one or both ends. The anterior end of the worm usually is more or less rounded, while the posterior end is characteristically pointed. Most species are small, measuring a few millimeters in length and a fraction of a millimeter in diameter; a few may reach more than a meter

in length. Nematodes usually are white or of a light pink color, but some parasitic species may be blood red due to ingested blood of the host. The body is covered by a hardened, non-cellular, glistening layer, the cuticle, which is characteristically marked by regularly arranged transverse markings or striations, often exceedingly fine. These striations are superficial and involve only the cuticle; there is no true segmentation. In some species the cuticle is longitudinally thickened, forming lateral sharp-edged expansions termed *alae*. These *alae* may extend the entire length of the body or may be confined either to the anterior or posterior portions of the body.

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The vital organs are suspended in the body cavity, which, lacking epithelium, is lined by a delicate connective tissue layer of mesenchymatous origin. The digestive tract consists of a straight tube connecting the extremities of the worm. The mouth is terminal at the anterior end of the body, and it may be surrounded by lips bearing sensory organs. The mouth is followed by a buccal cavity, an esophagus, intestine and a rectum terminating in a ventral terminal or subterminal anus or cloacal opening. The buccal cavity may be large or indistinguishable, and in some species it is supplied with teeth or rasps. The esophagus is a muscular structure with a triradiate lumen. It frequently terminates in a more or less conspicuous bulb or valvular apparatus. The intestine is composed of a single layer of epithelial cells which are covered by irregular muscle fibers and a connective tissue sheath. The rectum is lined with cuticle, as is the buccal cavity and the esophagus. In the male worm various developments of the dorsal wall of the cloaca give rise to accessory sexual structures such as spicules and the gubernaculum.

The excretory system of nematodes is varied and may be absent It frequently presents two lateral canals situated in the lateral chords connected with each other, anteriorly and ventrally by an excretory sinus The excretory sinus may lead into a reservoir lined with cuticle which in turn opens on the ventral surface through the excretory pore

The nervous system is composed of a circum esophageal ring the nerve center and a number of longitudinal nerves Branches of the main trunk terminate in all the important organs and the integument especially in sensory papillae and chemoreceptors Circulation and respiratory systems are not known for nematodes

The male reproductive system characteristically consists of a single tubular testis which empties into the vas deferens, which, in turn unites posteriorly with the rectum forming a cloaca A portion of the vas deferens may be expanded to form a seminal vesicle The female reproductive system consists of one or two elongated tubular ovaries connected with a uterus or uteri which terminate in the vaginal opening on the ventral surface of the body at the vulva

The simplest form of development is direct and is characteristic of free living nematodes Eggs produced by the female worm are retained within the uterus until fertilized by spermatozoa transferred to her by the male at copulation The newly hatched nematode resembles the adult in gross morphological characters but lacks a reproductive system and secondary sexual characters Further development to the adult stage is marked by various growth or larval stages terminated by molts the number of molts being four and the number of larval stages five Internal changes rarely occur to any marked degree until after the fourth stage is reached at which time the adult systems are formed

This type of development may be outlined as follows

Egg
First stage (larva)
(molt)
Second stage (larva)
(molt)
Third stage (larva)
(molt)
Fourth stage (larva)
(molt)
Fifth stage (adult)

The development of parasitic nematodes is essentially the same as that of free living forms with the exception that in the life cycle of the parasitic species there is a cessation of growth and development of the larva, usually upon reaching the third stage while awaiting an opportunity to gain access to a new definitive host Thus in most cases it is the third larva, a resting form which constitutes the infective stage Parasitic nematodes may pass through this period of waiting outside the body of the original host as (1) embryos within the eggshell (*Ascaris lumbricoides*, *Trichuris trichiura*, *Enterobius vermicularis*) (2) as free living but non feeding larvae (hookworms) or (3) as parasitic larvae in the body of an intermediate host an arthropod which frequently is obligatory (filarial worms) A striking exception to the usual waiting period outside the body occurs in the case of *Trichinella spiralis* This species is parasitic throughout its entire life cycle and passes its waiting period encapsulated in the flesh of the parental host

Infection with nematodes of the first category is acquired through fecal contamination In the second group infection results from direct contact with infected soil i e skin penetration by free living infective larvae is the usual mode of entrance into the host Infection with nematodes having obligatory development of the infective stage in an invertebrate host characteristically occurs at the time the invertebrate host usually an insect feeds on the definitive host Rarely the infection is acquired through ingestion of the parasitized invertebrate host Infection with nematodes parasitic throughout the life cycle results from ingestion of food i e flesh harboring infective larvae

The diagnosis of diseases caused by nematode parasites is often difficult Clinical signs and symptoms may be varied vague and misleading Immunological tests may be helpful but few are specific and their limitations must be kept in mind A positive diagnosis usually is made upon demonstration of certain characteristic stages of the parasite particularly eggs or larvae Familiarity with these stages and proper methods for their detection are essential for accuracy in diagnosis Sections of adult worms and larval forms frequently are present and may be prominent objects in stained tissue preparations The observer will recognize readily such portions of the parasite providing he has a general knowledge of nematode structure and histology The geographical distribution and the regional prevalence of a parasitic species and the opportunities for infection must be taken into account when nematodiasis is suspected in patients having had foreign travel or residence

NEMATODE INFECTIONS AND DISEASES ACQUIRED THROUGH FECAL CONTAMINATION

Three characteristic nematode parasites of man are acquired through fecal contamination, viz., (1) *Ascaris lumbricoides*, (2) *Trichuris trichiura* and (3) *Enterobius vermicularis* These helminths do not have

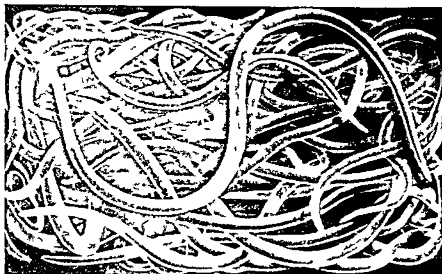


Fig 1 *Ascaris lumbricoides* Photograph of adult worms One male and numerous female specimens

an intermediate host or a vector Transmission from host to host is direct They are cosmopolitan parasites and their occurrence particularly in endemic form is indicative of a low level of sanitation and of unhygienic ways of living for the community

Ascariasis

Ascariasis in man is an infection with *Ascaris lumbricoides*, Linn., 1758 It is commonly called roundworm and stomach worm infection It characteristically occurs in children and young persons, less frequently in adults The adult parasite may be milk white or reddish yellow in color, and its body presents a definite sheen It is the largest of the human intestinal nematodes (Fig 1) The head bears three conspicuous lips surrounding a small buccal cavity (Fig 2) The females usually vary from 20 cm to 25 cm but may attain greater lengths with a diame

ter of about 3 mm The posterior extremity is straight The male worms are smaller and measure about 15 cm in length and about 3 mm in diameter The posterior end is characteristically bent forward ventrally and two short but prominent spicules may be seen protruding through the cloaca The eggs are oval with a thick transparent shell surrounded by an external albuminous coating which is coarsely mammillated

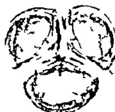


Fig 2



Fig 3

Fig 2 *Ascaris lumbricoides* Photograph of front view of an adult specimen showing the three lips surrounding central buccal cavity

Fig 3 *Ascaris lumbricoides* Photomicrograph of typical fertilized egg in fresh feces x 500

(Fig 3) They measure from 50μ to 75μ in length by 40μ to 50μ in breadth and are unsegmented at the time of deposition They are colorless when they leave the uterus of the female worm but during their short stay in the intestinal tract of the host the albuminous layer acquires a yellowish to deep brown color from bile Frequently eggs are passed without the albuminous coating as well as unfertilized eggs which are irregular in form and with the contents granular and without organization

The eggs of *A lumbriocoides* leave the host with the feces and under favorable conditions development of the infective stage is completed in about three weeks Infection results from ingesting the infective egg The eggs usually are carried directly to the mouth by hand less frequently with food or water They hatch a few hours after ingestion in the small intestine promptly penetrate the gut wall and then are carried passively by the lymph flow to the lungs Within the lungs they break into the alveoli where some further development and growth

take place, after which they actively migrate to the small intestine by way of the trachea esophagus and stomach[1] The worms become mature in the intestine, and their eggs appear in the stool in about two and one half months after exposure to infection Prenatal infection has been observed and may be of commoner occurrence than is generally realized

Symptomatology

The pathological effects from ascariasis may be quite variable, due in part to the fact the larval stages have an extensive course of migration in the body, and in part to the fact that the adult worms may also migrate from their normal habitat, the small intestine, into other organs and tissues In laboratory animals the migrations of ascaris larvae are known to produce lesions in the intestinal wall, liver, lymph nodes and especially in the lungs In breaking through the alveolar tissue into the alveoli the larvae produce small hemorrhages leading to severe inflammation In heavy infections in experimental animals the lungs may be extensively involved, becoming edematous hemorrhagic and consolidated Many larvae are destroyed in the tissues

In man severe pulmonary symptoms have been produced experimentally by feeding large numbers of infective ascarsis eggs, but in most natural infections it is extremely difficult to assign a definite symptomatology to the lung migration of ascarsis larvae[2] It is also difficult to define clearly the symptoms produced by the adult worms in the normal habitat, the small intestine Perhaps the commonest complaint is an intermittent intestinal colic with abdominal discomfort and loss of appetite Reflex nervous symptoms irritability insomnia and occasionally convulsions are noted commonly among heavily infected young children An eosinophil count of from 7 to 10 per cent is a characteristic symptom Frequently persons are sensitive to contact with the worms, particularly with the body fluid Among these symptoms are irritation of the eyes nose throat edema of the eyes and urticaria These allergic manifestations have occurred most frequently among biologists and students during laboratory studies of these parasites Asthma produced by adult *Ascarsis* with the attacks disappearing upon removal of the worms has been observed on several occasions[3] Also symptoms simulating epilepsy have disappeared after removal of these worms When occurring in great numbers, the worms may become entangled and thus cause intestinal obstruction by an acute mechanical occlusion Adult worms frequently leave the intestine, especially during febrile

disturbances, and wander into the stomach, esophagus nose ears and other unusual sites They may enter the bile ducts where their presence may be followed by abscess The adult worms may penetrate the intestinal wall causing peritonitis Such cases frequently are the result of infection with a single worm

Diagnosis and Treatment

Ascariasis frequently is detected by the patient upon discharge of adult worms with the feces or upon regurgitation The discharged specimen or specimens may represent the entire worm burden and search for further evidence of infection should be made and repeated if necessary before anthelmintic treatment is administered Usually definite diagnosis is established by finding eggs of the parasite in the feces (Fig 3) A single female worm daily produces so great a number of eggs that demonstration of them is certain by usual laboratory procedures

Crystalline hexylresorcinol (caprol ol) is recognized as the most efficient and safest ascaricide[4] It is available in 0 1 and 0 2 gm hard gelatine capsules The patient should eat only a light meal the evening before treatment and breakfast is omitted A preliminary purge is not required The dose of hexylresorcinol is 0 1 gm for each year of age up to 10 years the adult dose of 1 gm being given to those over 10 years of age A saline purge is given 2 hours after treatment Food should not be taken for 5 hours after treatment but otherwise the patient may follow his usual occupations The capsules must be swallowed not chewed since the drug may cause superficial erosion of the buccal mucosa Treatment may be repeated after 3 or 4 days if necessary Surgery may be required in intestinal obstruction or in biliary and peritoneal invasions.

Epidemiology

Ascaris lumbricoides has a world wide distribution It has been reported from within the Arctic circle and in regions where desert conditions prevail It is most abundant in tropical countries with heavy rainfall and is especially prevalent throughout the Orient Sporadic cases have been reported from practically every section of the United States but the parasite occurs endemically only in the southeastern states among the indigenous population of the Appalachian Mountains

and in parts of Louisiana and Florida. The family is almost always the unit of infection. Infected families usually are poor and of a low economic and social level. Ascariasis is a characteristic infection of children, the worm burden in adults being but a fraction of that in children. The lighter infection in adults is due largely to differences in habits which reduce the frequency to exposure.

As a rule the chief sources of infection are from eggs deposited by young children in the yards close to the house, under the house and sometimes within the house, areas in which children are accustomed to play. The eggs of the parasite are highly resistant to adverse conditions and such household pollution results in the accumulation of large numbers of eggs which are ingested by the children while playing in the dirt. Older children and adult members of the family customarily use whatever toilet facility is available or remove themselves some distance from the house to defecate. They are less frequently exposed to infection.

Most ascaris infections are light or of moderate intensity. Heavy infections are rare. Infected individuals living under endemic environments frequently pass adult worms and rapidly acquire new infection. In addition to the loss of adult worms many larvae are destroyed during their migration in the tissues. Therefore, the ingestion of large numbers of eggs is necessary to produce even moderate infection with adult worms and constant exposure to intense soil infection is necessary to produce heavy infection.

Therapeutic treatment is recommended for individual and sporadic cases and is important for the removal of dangerous worm burdens from heavily infected persons living in an endemic environment. Treatment alone however has little, if any value in the actual control of the parasite in endemic areas because of rapid reinfection. Control lies in the preventon of door yard pollution by young children.

Ascariasis commonly occurs in swine. Extensive research has shown no differences between the ascarids of man and swine in morphology or in physiological and biochemical relations. However, almost all attempts to infect healthy pigs with eggs from human sources have been unsuccessful and attempts to infect man with pig ascariasis has given negative results. The two forms are held to be distinct host varieties neither one being of any significance in the dissemination of the other.

Ascarids are common and universal parasites of domestic dogs and cats. These species have been reported a very few times from man but it is highly probable that the diagnosis of these cases were incorrect, or that they were spurious infections.

TRICHURIASIS

Trichuriasis in man is an intestinal infection with *Trichuris trichiura* (Linn., 1771) Stiles 1901 commonly known as the whipworm. The body of adult specimens strikingly resemble a whip, the posterior two-fifths being the handle and the anterior three fifths the lash. The larger posterior portion contains the vital organs. The delicate capillary esophagus provided with a terminal spear occupies the upper attenuated end. The male worm measures from 40 to 45 mm and the female from 45 to 50 mm in length. The posterior portion of the male is recurved and



Fig 4 *Trichuris trichiura* Photomicrograph of egg in fresh feces x 500

bears a barbed spicule. The eggs are characteristically barrel shaped (Fig 4). They have a thick brown shell with a prominent perforation at each end filled with a light colored plug. They measure from 51 to 59 μ in length by 22 μ in breadth and are unsegmented at the time of deposition. Man is the only proven host for *T. trichiura* but morphologically identical whipworms have been reported from swine and monkeys.

The whipworm is characteristically found with the anterior portion of the body threaded and interlaced in the epithelium of the intestine while the thick portion hangs free in the lumen. It is found most frequently in the cecum and the appendix, sometimes in the large intestine.

The development outside the body is similar to that of *Ascaris lumbricoides*. The development within the egg is slow and may require several weeks before the infective stage is reached. Upon ingestion the eggs hatch in the intestine and the young worms according to Hasegawa[6] penetrate the villi of the small intestine and remain quiescent

for several days Upon reaching maturity they return to the lumen of the intestine and migrate to the cecum, appendix and colon, their characteristic habitats

Trichuriasis usually is symptomless, and most cases would pass unnoticed except for the finding of the eggs upon fecal examination However, abdominal epigastric and lumbar pain, vomiting, constipation, fever, headache, anorexia, loss of weight and anemia were noted frequently by Swartzwelder[7] in a study of 81 uncomplicated clinical cases of trichuriasis In 36 of these cases appendicitis was listed as a tentative diagnosis No significant blood changes were noted The presence of the anterior portion of the worm in the tissues usually provokes no host reaction

The diagnosis of trichuriasis usually is made upon discovery of the eggs in the stool Flotation methods are preferred[3] *T trichiuris*, because of its position in the intestine is very resistant to the commoner anthelmintics but is effectively expelled by the fresh latex of certain wild fig trees which grow in Central America and parts of South America The latex of these trees, locally known as *leche de higueron*, usually is considered to be practically nontoxic and doses of 30 to 60 ml are administered[4] The active anthelmintic ingredient, a proteolytic enzyme, is lost in preservation Its use is therefore, limited geographically

Trichuris trichiura has a wide geographic distribution and is especially common in tropical and subtropical regions It is frequently associated with *Ascaris lumbricoides* and hookworm Its range is not as extensive as that of *A lumbricoides*, particularly in the temperate climates, and it does not occur in cold countries Usually where *Ascaris* and *Trichuris* are found together the incidence of *Trichuris* is lower

Field studies by Cort and Otto[8] have shown that in endemic trichuriasis the family is the unit of infection Its distribution according to age and sex is similar to that of ascariasis except that the peak of infection comes at a somewhat later age The human habits involved in the spread of *Trichuris* and *Ascaris* are apparently the same Differences in geographic and local distribution of these parasites apparently are due to differences of their eggs to environmental factors According to Nolf[9] the eggs of *Trichuris* are much less resistant to low temperatures than are those of *Ascaris*, and also somewhat less resistant to high temperatures They are also less resistant to desiccation and require more moisture for development than *Ascaris* eggs The incidence of *Trichuris* tends to be as great or greater than that of *Ascaris* only where there is a considerable amount of moisture in the soil with persistent moist areas about the

dwellings where eggs of the parasite are deposited Measures taken against ascariasis are equally effective against trichuriasis

Enterobiasis

Enterobiasis, or oxyuriasis, is an infection of the human intestine with the pinworm *Enterobius vermicularis* (Linn 1758) Leach 1853 It is sometimes known as the seatworm This parasite apparently is re-

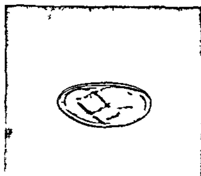


Fig 5 *Enterobius vermicularis* Photograph of embryonated (infective) egg x500.

stricted to man and it occurs in its various stages of development, from the lower ileum through the rectum It is chalky white in color The mouth is surrounded by three fairly distinct lips and the esophagus is provided with a prominent posterior bulb Narrow lateral *alae*, keel-like expansions of the cuticle are present and appear prominently in cross sections of the parasite The male is much smaller than the female and is easily overlooked unless special search is made for it It measures from 2 mm to 5 mm in length and the posterior third of the body is curved ventrally The tail is blunt The female measures from 9 mm to 12 mm in length and has a long, sharply pointed tail The body is characteristically rigid hence the common name pinworm The vulva is prominent and is situated in front of the posterior limit of the anterior third of the body The uteri in gravid specimens are greatly distended with eggs giving a plump appearance to the parasite The eggs are characteristically asymmetrical double-contoured and have colorless shells They measure from 50 to 60μ by 20 to 30μ and contain a more or less fully developed tadpole like embryo when deposited by the female worm (Fig 5)

The life history of *Enterobius vermicularis* is the simplest of any found among nematodes parasitic in vertebrates The gravid female worms do not ordinarily deposit their eggs in the lumen of the intestine but crawl out of the anus and deposit them in the perianal region (Fig 6) Contact with air is apparently a stimulus to oviposition The eggs are discharged by violent uterine contractions, and masses of eggs appear at the region of the vulva of the worm The spent female becomes shriveled and drops from the body of the host Within about six hours



Fig 6 *Enterobius* Female pinworm on perianal skin (Photograph by Cram)

after leaving the body of the female worm the eggs have developed a coiled larva (ring and a half embryo) which is infective These infective eggs may be readily transferred directly by hand to the mouth of the same host and indirectly to the same host or to new hosts through contamination of food and objects that can carry the infection Dust borne infection appears to be a very common occurrence

After ingestion the eggs hatch in the stomach or intestine The young pinworms live during the early part of their development in the lower part of the small intestine, cecum upper portions of the colon and frequently parasitize the appendix The fourth stage larva, a transient stage, burrows into the mucous membranes and returns to the lumen of the intestine upon reaching maturity After copulation the uteri begin to fill with eggs and the gravid female worms migrate down the rectum to discharge them in the anal region According to Schuffner[10] the duration of the cycle is from 37 to 53 days

Symptomatology

Clinical symptoms in pinworm infection are variable in both their nature and degree being apparently absent in some cases and severe in others[11] When present they are in most instances related to the migration of the adult worms and fourth stage larvae and less frequently to the younger forms Heavy intestinal infection may cause persistent diarrhea, dysentery and death[1]



Fig 7 Enterobiasis Photomicrograph showing cross sections of pinworms in the lumen of the human appendix Note characteristic lateral keel like expansions of the cuticle in each worm s ction

In migrating out through the anus the female worms may produce an intense itching and in long standing infections a severe anal pruritus may develop Distress due to anal pruritus is the commonest complaint[11] In female patients the worms may invade the genitalia Pinworm vaginitis appears to be of fairly frequent occurrence On numerous occasions degenerated female worms have been observed in the fallopian tubes

causing inflammation and symptoms of salpingitis[13] Pinworms have been observed also in the peritoneal cavity where they had become encapsulated in the peritoneum All such cases have been observed only during or after operation or at autopsy at which times the correct diagnosis was established Peritoneal infection with pinworms has never been reported in males

The role of the pinworm in appendicitis remains undetermined Botsford, Hudson and Chamberlain[14] express the opinion that the parasite may give rise to the syndrome of apendicitis without characteristic histological changes (Fig 7) According to Chandler[3] it is only the fourth-stage larva of *E vermicularis* that habitually burrows into mucous membranes (Fig 8) The transient nature of this stage of the pinworm in the wall of the appendix is not generally understood and probably accounts for the many failures to demonstrate the worm at operation

Bijlmer[12] reports a death due to enterobiasis in a man 46 years old with a history of prolonged and increasingly severe diarrhea and dysentery Postmortem examination revealed an invasion of thousands of immature pinworms probably fourth stage larvae, in the intestinal wall especially in that of the rectum but also in that of the colon and ileum Particularly striking were the many gangrenous ulcers with undetermined edges in the intestinal mucosa The presence of extensive tunnel formation indicates that the invasion occurred during the life of the patient

Diagnosis

Owing to the peculiar behavior of the gravid female worm during oviposition the usual methods of examination of feces are wholly inadequate and unreliable for detecting pinworm infection Thus far the most reliable means of diagnosis has been the finding of the eggs and worms collected in scrapings from the perianal skin Several technics have been recommended for obtaining the eggs, such as the use of spoons, glass tubes and rods spatulas and cotton pledgets of which the first practical and efficient procedure was devised by Hall[16] By Hall s method the tip of a glass rod is covered with a square of cellophane held in place on the rod by a rubber band The opposite end is carried through a rubber cork fitted into a glass tube which prevents drying and loss of material during transportation and ensures safety of the carrier from infection The swab has been generally referred to in the literature as the NIH (National Institute of Health) swab

To obtain a specimen for examination, the cellophaned end of the swab is passed radially along the perianal folds Subsequently the piece of cellophane with the scrapings adhering to it is removed from the glass rod and placed face down over two drops of physiological saline solution and examined under the microscope In addition to eggs of the parasite, vestiges of female worms or whole female worms may be present in the scrapings Swabs should be taken during the night or in the morning before the patient bathes or defecates preferably on at least seven days if the first results are negative



Fig 8 Enterobiasis Photomicrograph showing pinworm invasion of human appendix with abscess formation A longitudinal section through the esophageal region of the worm is shown deeply embedded in the tissue

The Scotch cellulose tape swab introduced by Graham[17] is equally effective in detecting pinworm infection and simpler in operation A strip of tape 3 to 4 cm in length held adhesive side out over the closed end of a test tube or wooden tongue depressor is firmly applied to the perianal skin The tape is then placed adhesive side down on a glass tube for direct microscopic examination Pinworms are discovered frequently after an enema has been given or upon examination of the perianal skin in the morning before bathing (Fig 6) The microscopic

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examination of nail dirt may reveal pinworm infection, but accord to Schuffner and Swellengrebel[18] it is not reliable and should not repl examination of the perianal region In stained preparations of infec tissue the parasite when seen in cross section, may be readily identi by the lateral keel like expansion of the cuticle

Treatment

Small enemas are recommended by Schuffner[9] for the removal worms in light infections but high enemas given with the object getting at the immature worms higher in the intestine are held to superfluous and often disturbing to the patient These worms are b eliminated by anthelmintic treatment Wright, Brady and Bozicevic recommended gentian violet medicinal for the treatment of pinwor reporting a cure rate of over 90 per cent It is now held the drug choice For adults the recommended dose is 0 065 gm (1 gr) of t drug in a water-soluble, coated, four-hour type tablet given 3 tin daily before meals for a period of 8 days followed by a 7 day r period after which treatment is repeated for 8 additional days F children the recommended daily dosage is 0 01 gm (1/6 gr) for ea year of apparent age According to the authors cited above, the dru in general, is well tolerated Contraindications include concomita ascaris infection any disease of the gastrointestinal tract, cardiac, hepat or renal disease and pregnancy Treatment should be repeated up the first positive sign of infection

The prognosis is good Gain in weight, improvement in color d appearance of dark circles under the eyes improved appetite and pa ticularly improved social attitude and scholastic standing have bee reported in children following successful treatment[9]

Epidemiology

Enterobiasis is a cosmopolitan infection Recent critical studies hav shown that it may occur in about 20 per cent of the general populatio of the United States The negro race has a lower incidence than th white race The incidence is highest in children of school age, nex highest in those of pre-school age and lowest in adults The school i apparently the determining factor in these differences The infectio in males frequently is somewhat higher than in females

Crowding is an important factor in the spread of enterobiasis, an

the family frequently is the unit of infection Under institutional conditions the incidence of infection is lower among children occupying rooms with one or two beds than where larger groups are quartered in dormitories

The control of pinworm infection often is difficult Dust borne eggs are known to be an important source of infection Nolan and Reardon[1] studied the distribution of pinworm eggs in household dust from seven homes, in each of which at least one member of the family was heavily infected Viable eggs were found in dust taken from the floor and furniture and from moldings of doorways and ceiling lights D Antoni and associates[2] obtained similar results from their study at six institutional homes for children Viable eggs were found in all samples of dust collected in the dormitories from floor cracks ledges of pillars of doors windows and toilet partitions at heights under 8 feet from the floor Schuffner[10] found 119 *Enterobius* eggs on about 1 square foot of surface in a large dining hall of a school in Amsterdam Holland and about 5 000 *in small closets Dust borne infection usually is light and particularly* favors the dissemination of the parasite Severe enterobiasis arises primarily from finger borne infection whereby thousands of eggs may be ingested at one time

The wearing of closely fitted night clothes and bathing shower preferred immediately upon rising in the morning will aid in preventing the finger mouth route of infection Air borne infection may be greatly reduced through careful handling of bedding and night clothes of infected persons, since eggs may be spread from these into the air by bed making

Specific treatment should be administered simultaneously to all infected persons within a household and the treatment repeated upon the first evidence of re infection According to Schuffner[1] if eggs appear in less than 37 days after specific treatment the drug has failed and if eggs appear between 37 and 53 days after treatment the drug may have been successful but probably a new dust borne infection may have occurred If eggs appear after the 54th day a new infection must have occurred

NEMATODE INFECTIONS AND DISEASES ACQUIRED THROUGH CONTACT WITH INFECTED SOIL

Anclyostomiasis caused by the hookworms *Anclyostoma duodenale* and *Necator americanus* and strongyloidiasis caused by *Strongyloides*

examination of nail dirt may reveal pinworm infection, but according to Schuffner and Swellengrebel[18] it is not reliable and should not replace examination of the perianal region In stained preparations of infected tissue the parasite, when seen in cross section may be readily identified by the lateral keel-like expansion of the cuticle

Treatment

Small enemas are recommended by Schuffner[9] for the removal of worms in light infections but high enemas given with the object of getting at the immature worms higher in the intestine are held to be superfluous and often disturbing to the patient These worms are best eliminated by anthelmintic treatment Wright, Brady and Bozicevich[19] recommended gentian violet medicinal for the treatment of pinworms reporting a cure rate of over 90 per cent It is now held the drug of choice For adults, the recommended dose is 0 065 gm (1 gr) of the drug in a water soluble, coated four hour type tablet given 3 times daily before meals for a period of 8 days, followed by a 7 day rest period, after which treatment is repeated for 8 additional days For children the recommended daily dosage is 0 01 gm (1/6 gr) for each year of apparent age According to the authors cited above, the drug in general, is well tolerated Contraindications include concomitant ascaris infection, any disease of the gastrointestinal tract cardiac, hepatic or renal disease and pregnancy Treatment should be repeated upon the first positive sign of infection

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Crowding is an important factor in the spread of enterobiasis, and

Hookworm disease is a clinical syndrome caused by infection with *Ancylostoma duodenale* (Dubini 1843) Creplin 1845 and/or *Necator americanus* (Stiles, 1902) Stiles, 1906 Hookworm infection usually implies the harboring of few hookworms in the intestine without symptoms The *Ancylostomidae* or the hookworms are distinguished from other members of *Strongyloidea* by the presence of a well developed buccal capsule bearing ventral teeth cusps or cutting plates on its anterior margin

Ancylostoma duodenale and *Necator americanus* are the only true and characteristic hookworms of man Both species have been reported incidentally in other hosts but there is no good evidence that animals may serve as true or important reservoir hosts for human hookworm infection *Ancylostoma braziliense* and *Ancylostoma caninum*, two common hookworms of cats and dogs very rarely cause intestinal parasitism in man The infective larvae of these species will however invade human skin, causing a dermatitis known as creeping eruption

The males of *Ancylostoma duodenale* measure about 10 mm in length by 0 45 mm in diameter, the females 12 mm in length by 0 6 mm in diameter *Necator americanus* is somewhat smaller the males measuring about 8 mm long and the females 10 mm long Both are of a pale flesh color, more or less reddened posteriorly and have rigid bodies There is a marked torsion of the body so that the anal opening is placed laterally with reference to the bending of the head end The cup shaped buccal capsule of both species is bent dorsally That of *A duodenale* shows one pair of dorsal and two pairs of ventral teeth that of *N americanus* shows chitinous plates at the sides of the capsule but no hook like teeth There are also certain gross differences between *A duodenale* and *N americanus*, whereby they can be distinguished readily without the use of the microscope In *Ancylostoma* the curvature of the body corresponds with the bending of the anterior extremity while in *Necator* the curvature of the body is the reverse of that of the head end (Fig 9) In the former species the female genital opening is posterior to the middle of the body while in the latter it is anterior The males also show characteristics by which they may be readily identified The spicules of *Ancylostoma* are needle pointed while those of *Necator* show a single terminal barb The main points of difference in these two species are given in the accompanying table

stercoralis, are classical examples of nematode diseases of man acquired through direct contact with infected soil Skin penetration by infective, free-living third-stage larvae is the usual mode of access of such parasites to the host, but infection by mouth and prenatal infection can occur also

The hookworms belong to the superfamily, *Strongyloidea*, a large and very important group in both human and veterinary medicine It consists entirely of parasitic forms Members of this group are relatively small nematodes the males of which bear a prominent caudal bursa, a prehensile sort of expansion of the cuticle, supported by finger like rays extending outward from a common center *Strongyloides stercoralis* bears no close morphologic resemblance to the hookworms It belongs



Fig 9 Silhouettes of the hookworms of man showing their individual shapes and characteristic attitudes and the position of *Ancylostoma duodenale* and *Necator americanus* assume *in copula* (After Lane)

to the superfamily *Rhabditoidea*, a nematode group containing free living forms and facultative and obligatory parasites Among the obligatory parasites of this group, including *S stercoralis*, there is a marked tendency for an alternation between free-living and parasitic generations with a suppression of males in the parasitic generation

Ancylostomiasis

Ancylostomiasis or uncinariasis is an intestinal infection with nematodes of the family *Ancylostomidae*, commonly known as hookworms

Ancylostoma braziliense is widely distributed throughout the tropics It is a common parasite of cats less frequent in dogs in the southern United States but natural infection in the United States probably does not occur north of Maryland *Ancylostoma caninum* has a geographical distribution similar to that of *A braziliense* in tropical zones but has a wider range in countries with cooler climates It is an important parasite of dogs in the United States as far north as New Hampshire

Modern knowledge of ancylostomiasis in man dates from the description of *Ancylostoma duodenale* by Dubini in 1843 In 1878 Grassi and colleagues discovered that hookworm infection could be detected by



Fig 10 Photomicrograph of a hookworm egg in fresh feces x 500

fecal examination for eggs Clinical hookworm disease was first recognized as such in 1880 by Perroncito in laborers who were constructing the Saint Gothard tunnel through the Alps. Leichtenstern in 1887 demonstrated experimentally that infection could be brought about by the ingestion of larvae and Looss in 1898 in Egypt discovered that hookworm larvae penetrate the skin In 1904 Looss demonstrated the route of migration and the consecutive stages of development of the parasite from the site of entrance through the lungs and to the small intestine In 190 a new hookworm species *Necator americanus* was reported from Puerto Rico and southern United States Much of the anemia in these countries was attributed to infection with this species and interest in hookworm shifted to the Western Hemisphere

The pioneer work of Ashford and Gutierrez [1] in Puerto Rico and that of Stiles in the United States led to the creation of the Rockefeller Sanitary Commission in 1909 for the distinct purpose of combating hook

Table I

Differential Characters of *Ancylostoma duodenale* and *Necator americanus*

A. duodenale	*N. americanus*
1 Head continues in same general curve of body	1 Head turned contrary to general curve of body giving a permanent hooked appearance to anterior end of the worm
2 Buccal capsule with two pairs of hook-like teeth about equal in size	2 Buccal capsule without teeth but with one pair of cutting plates
3 Vulva posterior to middle of body	3 Vulva anterior to middle of body
4 Small spine at posterior extremity of female	4 No spine at posterior extremity of female
5 Bursa copulatrix fan shaped	5 Bursa copulatrix more rounded
6 Dorsal ray of bursa tripartite	6 Dorsal ray of bursa bipartite
7 Larger than *Necator*	7 Smaller than *Ancylostoma*

Ancylostoma braziliense is the smallest of the species of *Ancylostoma*, the males measure about 8 mm in length by 0 3 mm in diameter and the females 9 mm by 0 4 mm The species may be identified by the relatively small buccal capsule have a pair of small median teeth and a pair of larger, prominent outer teeth *A caninum* approximates *A duodenale* in size Its buccal capsule is relatively wide and has three pairs of ventral teeth

There is no marked specific difference in the eggs of the different species of hookworms They have a thin, smooth colorless shell, composed of two layers the chitinous shell externally and the delicate vitelline membrane internally They measure about 60 μ in length by 40 μ in breadth and are in an early segmentation stage when discharged (Fig 10)

Ancylostoma duodenale occurs in practically all countries which lie in tropical and subtropical zones It is the only hookworm of man in the Mediterranean area Egypt and northern parts of India, China and Japan *Necator americanus* also has wide geographical distribution It occurs alone in central and south Africa the south eastern United States, in parts of South America and in some islands of the West Indies Both species are found together in parts of Central and South America the West Indies and the Orient, but *N americanus* is invariably the commoner parasite[3]

cuous defecation on the ground by infected persons and unsanitary methods of excreta disposal

Development of hookworm larvae can be completed at temperatures ranging from 12 to 37 C with the optimum from about 25



Fig 11 Characteristic attitudes of infective hookworm larvae on moist soil

to 30 C The eggs and larvae are quickly killed in temperatures close to freezing The injurious effect of low temperatures on the free living stages is the determining factor in limiting the distribution of hookworm diseases to the tropical and subtropical countries The eggs and larvae are quickly killed also by dessication Therefore in regions within the tropical belt having little rainfall and without irrigation hookworm

worm disease That organization was followed in 1914 by the establishment of the International Health Board of the Rockefeller Foundation which, for years following cooperated with governments throughout the world in hookworm control The incidence of hookworm disease has been greatly reduced in most countries where intensive control campaigns have been conducted, but the disease is still of public health importance in many tropical countries and parts of the United States

The life histories of all species of hookworm are essentially the same The eggs are deposited in the lumen of the small intestine and make their exit with the feces Under favorable conditions of oxygen, moisture and temperature the eggs develop and hatch in about 24 hours The first-stage larvae is about 250 μ long and has an elongated buccal cavity and a club shaped esophagus with esophageal valves Because of the character of the esophagus this stage is referred to as a rhabditiform larva It feeds upon bacteria in the deposited feces and undergoes its first molt in about 48 hours after hatching The second stage larva is about twice the size of the first-stage but otherwise shows no striking difference in morphology After two more days of active feeding and the storing of food in the cells lining the intestine this larva ceases to feed, undergoes a second molt and thereupon enters the third or infective stage The cuticle at this molt is normally retained as a protective sheath, but occasionally it may be shed The morphology of the infective stage is quite different from that of the preceding stages The tail is shorter, and the esophagus is more uniform in width with tapering of the anterior portion and the esophageal valves are lacking The anterior portion of the lumen of the mouth is closed It is often referred to as a filariform larva because of the elongated shape of the esophagus

Skin penetration by infective larvae is the usual mode of infection Penetration is accomplished in a few minutes when the larvae have leverage as in mud or in an evaporating film of moisture, but they are not able to penetrate the skin when submerged in water The third molt is completed on the skin of the host and within a few hours later they are in the subcutaneous tissue They enter the lymphatics, some probably enter the blood vessels directly, and are carried to the lungs They break through the lung tissue into the alveoli and travel up the trachea The larvae then are swallowed and pass through the stomach and on to the small intestine where they grow to maturity When infective larvae are swallowed they pass directly to the small intestine foregoing the lung migration [6] Eggs first appear in the feces about the fifth week after infection (Fig 10) Soil infection results from promis

itch occurs most frequently on the feet particularly between the toes for it is these parts which are exposed to larva laden earth The lesions resulting from a single exposure may persist for a week or ten days Its occurrence often is seasonal corresponding to periods when both temperature and humidity are favorable for the development and maintenance of soil infection

Adult hookworms feed chiefly upon elements derived from the blood (Fig 12) They bite deeply into the mucosa causing small hemorrhages, the bleeding being maintained by the deposition in the wound of a secretion by the parasite which inhibits coagulation of the blood The worms move from place to place and when there are many present the daily blood loss may be considerable They occasionally invade the submucosa and sometimes the muscularis of the small intestine causing destruction of tissue and hemorrhage and leading to concomitant inflammatory reactions The hemorrhagic lesion usually contains but a single worm eggs in various stages of development and sometimes larvae Respiratory symptoms particularly bronchitis may be produced by the migrations of these larvae through the lungs but these are probably experienced only after an extremely heavy exposure

Most light intestinal infections produce no recognized symptoms While it is not possible to indicate definitely the actual number of worms necessary to produce clinical symptoms it has been observed that persons estimated to harbor close to 100 hookworms (*Necator americanus*) usually present no measurable injury that can be attributed to the presence of the parasites[30, 1] Clinical hookworm disease usually is associated with a heavy worm burden frequently amounting to several thousand worms The most frequent mild symptoms are pallor of skin and mucous membranes listlessness and increased susceptibility to common illnesses In more severe cases the conjunctivae and mucous membranes become blanched finally assuming a light sepia or yellowish tinge Light patches may appear on the mucosa of the soft palate Subcutaneous puffiness under the eyes above the wrists and ankles and on the backs of the hands and tops of the feet are not uncommon These cases show from 4 to 5 million red blood cells per cubic millimeter the hemoglobin values are from 60 to 80 per cent and there may be slight eosinophilia General muscular weakness edema of the face and extremities tachycardia cardiac murmurs and enlargement of the heart winging of the scapulae and loss of subcutaneous fat and muscle tonicity are associated with advanced and severe hookworm infections Blood studies in these generally have shown red cell counts from 2 to 3

infection is absent or kept at a low level. Loose, sandy or loam soils that are well shaded are particularly favorable for larval development of hookworms, whereas heavy clay soils are unsuitable.[7] Intense soil infection has been observed in sugar cane fields, in coffee and in cultivated mulberry groves where the soil is characteristically of a light texture with deep shade prevailing.[8]

When the rhabditiform larvae develop into the infective stage, they acquire tropisms peculiar to this period. They migrate vertically to the very top soil particles from which they extend themselves singly or in polyp-like masses with the support of the surface film of soil water. So dominant is the upward movement that the larvae remain practically at the spot where the infected feces was deposited, unless disseminated by outside agencies, animals or washing rains, for this reason a particular spot may contain thousands of infected hookworm larvae, whereas another spot one foot away may be entirely free of them. This characteristic position of the infective larvae in moist soil is most advantageous to the parasite in its transfer to the bare foot of persons walking through an infected area (Fig. 11).

The infective larvae are markedly thermotropic and when transferred to the bare foot or other exposed parts of the body their activity is greatly aroused and almost immediately they begin boring into the skin.

Unless an infective larva successfully enters man its length of life is limited by the supply of food stored in its intestinal cells, providing other factors are favorable. In water under laboratory conditions larvae have been kept alive for as long as eighteen months. In the soil, however, under natural conditions, frequent droughts, changing temperatures, heavy rains and natural enemies such as bacteria, protozoa and fungi are continually acting upon them, and their numbers become greatly reduced within a short time. A few of a given lot may survive for several months in nature, but it is doubtful if these have sufficient vitality to gain entrance to their host when such an opportunity presents itself.[9] The death rate of a given lot of larvae is always greatest within the first ten days.

Symptomatology

The penetration of the infective hookworm larvae through the skin produces lesions which are commonly known as ground itch. Secondary bacterial infection may increase the severity of this condition. Ground

of 1 18 may be substituted for sodium chloride. This method is not quantitative.

Various methods have been developed for estimating worm burdens. Of these Stoll's technique[33] has been used most widely in determining the clinical importance of hookworm infection in population groups and for the evaluation of control measures. This technique is in some respects similar to a blood count, i.e. (1) a measured quantity of feces is taken as a sample, ( ) it is diluted in a constant volume of fluid and (3) a measured sample of a homogeneous suspension is examined. The counting method is essentially a dilution. The procedure is as follows:

1. Fill the special Stoll flask with 0 1 normal sodium hydroxide to the bottom mark etched on the neck of the flask (56 c.c.). Using an applicator, add sufficient feces to the fluid to raise the level to the upper mark etched on the neck (60 c.c.).
3. Add 6 to 8 glass beads and firmly insert a No. 4 rubber stopper.
4. If the feces is very hard, allow the preparation to soak for a while.
5. Shake vigorously with a straight up and down motion for one minute to secure a *homogeneous suspension*. It is important to avoid a circular motion since this may concentrate the ova in a small area, defeating the purpose of the shaking. Routinely it is best to run the sample to this point in the afternoon and set it aside until the next morning. Then reshake the contents of the flask the following day and proceed.
6. With a pipette calibrated to 0 15 c.c. and supplied with a rubber bulb, *quickly* withdraw such a measured sample, inserting the tip of the pipette to the center of the flask.
7. Expel the entire contents of the pipette on to a 3 × [illegible] inch slide.
8. Cover the drop with a [illegible] × 40 mm No. [illegible] coverslip.
9. Examine under low power of the microscope, moving the slide with a mechanical stage.
10. Count *all* the hookworm ova present in the preparation.
11. Multiply the number obtained by 100. This will yield the total number of ova per c.c. of formed feces. For mushy stools multiply this latter number by the correction factor 2, for diarrheic stools by 4.

It has been considered by various workers that when there is a worm burden of 100 or more hookworms (*Necator americanus*) clinical symptoms are likely to occur. This intensity level is represented by 600 or more eggs per c.c. of feces.

million and 10 to 50 per cent hemoglobin levels The eosinophil count usually does not exceed 12 per cent, but eosinophilia may be absent Puberty may be delayed, and mental development is retarded

Chronic hookworm disease, however, seldom results from uncomplicated hookworm infection Hookworm disease is produced by hookworm infection plus malnutrition resulting from inadequate diet, concomitant parasitism (frequently malaria) and other debilitating factors resulting from poor living



Fig 1 Ancylostomiasis Longitudinal section through the anterior portion of an adult worm showing its attachment to the intestinal mucosa and the effects of suction produced by the esophagus

Diagnosis

The diagnosis of hookworm infection is based upon the demonstration of eggs in the feces (Fig 10) Specific diagnosis is based upon the identification of worms, usually obtained following anthelmintic treatment Concentration methods should be employed to reveal the ova Willis' method[3] (modified) is one of the easiest to follow and is one of the most accurate of the simple methods In this technique approximately 1 gm of feces is emulsified thoroughly with a small amount of sodium chloride solution having a specific gravity of at least 1 0, in a cylindrical container with a capacity of approximately 20 c c The container is then filled with salt solution and gently stirred A grease free 3 x 2 inch slide is applied to the top of the container in contact with the meniscus without air pockets or without overflow The preparation is allowed to stand for about 15 minutes The slide is then removed carefully inverted and examined microscopically for ova before the preparation begins to dry Zinc sulfate solution having a specific gravity

canum) is characteristically less severe in the negro race than in the white possibly due to a true racial immunity in the former

Since the spread of hookworm disease is due entirely to neglect of sanitation its prevention and control requires the installation of adequate latrine accommodations and the habitual use of them by the people who are to be directly benefited Therapeutic treatment relieves immediate suffering but without sanitation the benefit of such treatment is transient A single anthelmintic treatment seldom removes all hookworms and several treatment may be required before the patient is negative by stool examination Public health control measures are therefore aimed to reduce the worm burden to a subclinical level by medication and control through improved sanitation In clinical practice all persons harboring hookworms no matter how few in number should be treated re examined a week later and treatment repeated if examination gives positive findings

Creeping Eruption

The name *creeping eruption*, *larva migrans* and *dermatitis linearis migrans* have been associated for many years with skin lesions caused by the active migration in the dermal tissues by animal parasites particularly fly larvae mites ants[37] and larvae of the nematode *Gnathostoma spinigerum*[38] Another and more frequent cause of this disease is the third stage larva of the cat and dog hookworms, *Ancylostoma braziliense* and *A caninum*[37] Creeping eruption is prevalent in certain regions of southern United States particularly Florida the Carolinas Georgia Alabama and Texas and infection (*A caninum*) has been acquired as far north as Boston Massachusetts[39] It has been observed also in Africa[40] but natural infections appear to be rare in the Philippine Islands[41] and probably in other oriental countries It characteristically occurs in white persons and rarely among negroes

Skin Lesion

The disease as seen in the South is characterized by a linear tortuous serpiginous eruption occurring on areas of the skin coming in contact with the soil The most recent portion of the track left by the larva is represented by a thin reddish line which later becomes elevated and palpable The lesion may extend from a few millimeters to several centi

Treatment

Tetrachlorethylene probably is the drug of choice in uncomplicated hookworm infection[1] If ascaris infection is present, the ascarids should be removed by hexylresorcinol before treatment for hookworms is administered For adults the recommended dose of tetrachlorethylene is 3 ml and for children 0 2 ml for each year of age The drug is best administered in early morning on empty stomach in hard gelatine capsules Purgation with Glauber salts (sodium sulphate) is recommended on the night before treatment, following a light evening meal Saline purgation should follow within 1 or 2 hours after administration of the drug Absorption of tetrachlorethylene is negligible and toxic manifestations are rare except for headache and vertigo which disappear following post-treatment purgation Treatment may be repeated in a week or 10 days if necessary

Symptoms of hookworm disease can be temporarily relieved by the use of iron therapy Recovery and the return to normal hemoglobin levels usually are slow when treatment consists of worm removal without the addition of iron therapy Rapid improvement results with the combined use of anthelmintics iron therapy and improved diet[31]

Epidemiology

The relative intensity of hookworm infection in the sexes and in different age groups varies greatly in different populations Usually however infection is very light or absent in children under 3 years of age it gradually increases up to 10 years and reaches the adult level somewhere in the early teens or somewhat later The infection in males usually is heavier than in females due to differences in habits and occupations The most important sites for infection are protected places not far from the dwellings, preferred places for defecating by adults and older children Young children habitually defecate very close to their dwellings where conditions are usually unfavorable for development or hookworm larvae Infection in children usually starts when they begin to visit adult defecation places

Hookworm disease occurs most frequently in rural areas, but in general it is not related to any particular type of agriculture However conditions in coffee and mulberry cultivation are highly favorable for hookworm dissemination[14, 36] Hookworm infection (*Necator ameri*

caninum) is characteristically less severe in the negro race than in the white possibly due to a true racial immunity in the former

Since the spread of hookworm disease is due entirely to neglect of sanitation its prevention and control requires the installation of adequate latrine accommodations and the habitual use of them by the people who are to be directly benefited Therapeutic treatment relieves immediate suffering but without sanitation the benefit of such treatment is transient A single anthelmintic treatment seldom removes all hookworms and several treatment may be required before the patient is negative by stool examination Public health control measures are therefore aimed to reduce the worm burden to a subclinical level by medication and control through improved sanitation In clinical practice all persons harboring hookworms no matter how few in number should be treated re examined a week later and treatment repeated, if examination gives positive findings

Creeping Eruption

The name *creeping eruption, larva migrans* and *dermatitis linearis migrans* have been associated for many years with skin lesions caused by the active migration in the dermal tissues by animal parasites, particularly fly larvae mites ants[7] and larvae of the nematode *Gnathostoma spinigerum*[8] Another and more frequent cause of this disease is the third stage larva of the cat and dog hookworms, *Ancylostoma braziliense* and *A caninum*[31] Creeping eruption is prevalent in certain regions of southern United States particularly Florida the Carolinas Georgia Alabama and Texas and infection (*A caninum*) has been acquired as far north as Boston Massachusetts[39] It has been observed also in Africa[40] but natural infections appear to be rare in the Philippine Islands[41] and probably in other oriental countries It characteristically occurs in white persons and rarely among negroes

Skin Lesion

The disease as seen in the South is characterized by a linear tortuous serpiginous eruption occurring on areas of the skin coming in contact with the soil The most recent portion of the track left by the larva is represented by a thin reddish line which later becomes elevated and palpable The lesion may extend from a few millimeters to several centi-

The most satisfactory treatment for creeping eruption has been local freezing, applied to the skin in the advancing area of the lesion Either carbon dioxide snow or ethyl chloride spraying may be used A bi yearly fecal examination of pet dogs and cats, with anthelmintic treat ment to those found positive for hookworms, would provide a practical precautionary measure

Strongyloidiasis

Strongyloidiasis is caused by infection with nematodes of the genus *Strongyloides* This genus is widely represented among the vertebrates, particularly among mammals All species are strikingly similar in mor phology and usually lack host specificity, but experimental and epidemi ological studies support the view that each is a valid species[4] and that only *S stercoralis* (Bavay, 1877) Stiles and Hassall, 1902 is important for man

The intestinal form of *S stercoralis* is a colorless, transparent female worm approximately 2 5 mm in length and 40 μ in maximum diameter The body tapers anteriorly and ends in a short conical tail The esophagus is long and slender and conspicuously occupies the anterior fourth of the body The vulva is located near the posterior third of the body and leads directly to the uterine branches which are opposed The uteri contain from eight to fifteen segmenting and embryonated thin shelled eggs characteristically arranged in single file The occurrence of parasitic males was reported[43,44] but has not been confirmed by other workers The female worm generally is held to be parthenogenetic

The parasitic females live more or less deeply embedded in the mucous membrane of the small intestine in which the eggs usually are deposited and promptly hatch The first larvae are rhabditiform and resemble those of hookworm except for the very short and narrow buccal cavity Normally, these larvae leave the host with the feces and then begin to feed and grow as free-living forms From this point, however, they may follow either one or two courses of development, known respectively as (1) the direct or homogonic type and (2) the indirect or heterogonic type

In the homogonic type the rhabditiform larvae after two molts develop into filariform or infective larvae within about 24 hours These larvae are unsheathed They resemble the corresponding stage of hook worm except for a longer esophagus which occupies the anterior half of the body, and a notched caudal extremity and their behavior in the

soil also is similar to that of infective hookworm larvae In the heterogonic type of development the rhabditiform larvae, instead of developing into infective larvae, grow into adult free living males and females The fertilized females produce eggs which hatch soon after being deposited The first stage is a rhabditiform larva morphologically identical to those hatching from eggs produced by the parasitic female Again, after two molts, these larvae become filariform larvae There may be several generations of free living bisexual forms with increasing numbers of filariform larvae appearing in each successive generation

Auto-infection with complete elimination of a free living stage[1, 46] may occur Rhabditiform larvae produced by the parasitic female may develop into small filariform larvae in the intestine which reinfect through the walls of the ileum or colon

The filariform larvae of *S stercoralis* normally penetrate the skin but *oral infection may occur The young worms entering the skin are* carried to the lungs as are hookworm larvae where considerable development takes place They then leave the lungs pass up the trachea are swallowed and upon reaching the intestine invade the mucosa become mature and produce eggs

Symptomatology

The first lesions caused by the parasite occur at the site of entry of the infective larvae into the skin Intense pruritus may develop but usually the lesions are much less severe than those caused by infective hookworm larvae Larvae migrating through the lungs may cause hemorrhage and cellular infiltration into the alveoli and bronchioles Larvae which fail to complete the normal migration may become mature in the bronchial epithelium and set up foci of infection with the production of larval progeny Most of the young worms which reach the intestine invade the mucosa and submucosa of the duodenum and upper jejunum and soon produce eggs The migrations of the female worms through the mucosa and the passage of larvae to the lumen of the intestine produce a mechanical, and possibly a lytic destruction of the tissue with inflammatory changes In heavy infections extensive honeycombing may result with ulceration and sloughing (Fig 14)

Light infections probably are asymptomatic in most instances Early symptoms characteristically include intermittent attacks of diarrhea and epigastric distress In chronic and severe cases probably the result of hyperinfection diarrhea and sometimes dysentery may become persist-

ent and intractable The patient may become neurasthenic anemic and emaciated Recurring urticaria has been observed in long standing, uncomplicated infections

Diagnosis

Diagnosis of the strongyloidiasis is based on the discovery of larvae, usually the first or rhabditiform larva, in freshly passed feces If the

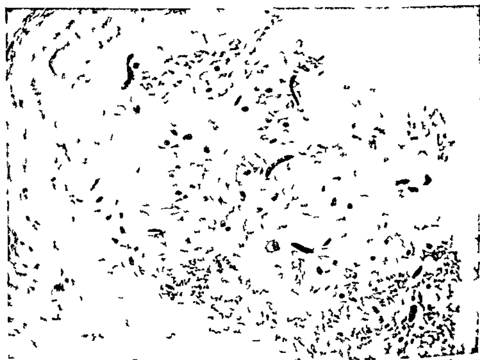


Fig 14 Fatal strongyloidiasis in man Massive invasion of the jejunum resulting in denudation and erosion of the mucous coat to the muscularis mucosae

infected stool is held for 24 hours at room temperature, filariform larvae or free living adult worms may be demonstrated The prognosis is good in most cases but strongyloidiasis should always be regarded as a potentially dangerous infection

Treatment

The drug of choice in the treatment of strongyloidiasis is gentian violet medicinal Most cases respond satisfactorily when the drug is

administered as recommended for enterobiasis but tablets with a one and one half hour coating are preferred In refractory cases of intestinal strongyloidiasis a single transduodenal intubation of 25 ml of a 1 per cent aqueous solution of gentian violet medicinal powder usually is efficient For pulmonary strongyloidiasis and for severe late stage intestinal cases[47] intravenous injection of 5 ml of a sterile 0 5 per cent aqueous solution of the drug may be given every third day for as many as 8 injections

Epidemiology

The geographic distribution of human strongyloidiasis closely parallels that of hookworm infection but sporadic cases of strongyloidiasis have been observed far beyond hookworm confines Cadham[48] reported a severe infection acquired in Winnipeg Canada and a similar locally acquired infection was observed in Boston Massachusetts[49] in an institutional environment Measures used against hookworm infection are equally effective against strongyloidiasis

NEMATODE INFECTIONS AND DISEASES TRANSMITTED BY ARTHROPODS

FILARIASIS

Filariasis is an infection with nematode parasites of the superfamily *Filarioidea*, in which clinical manifestations may be either present or absent These parasites are commonly known as filarial worms The adults or parental forms of this group are long and thread like They are characteristically tissue parasites inhabiting the lymphatics blood vessels connective tissue or serous cavities of land vertebrates namely frogs lizards birds and mammals The progeny of the adult worms are motile larvae and because of their minute size are known as microfilariae These microfilariae are deposited with or without periodicity *within the body of the host and must escape through the skin during* the feeding of a blood sucking insect for further development and transmission to a new host Whereas adult filarial worms are markedly host specific the ability of microfilariae to develop in a wide range of blood sucking arthropods particularly mosquitoes is a prominent feature of the group The parental forms of most species of filarial worms

ınfectıng man have been studıed by relatıvely few workers They rarely enter ın the dıagnosıs Specıfic dıagnosıs usually ıs establıshed on morphologıcal and bıologıcal characters of the mıcrofilarıae

Of the great number of specıes of filarıal worms only *Wuchererıa bancroftı* (Cobbold, 1877), Seurat, 1921, *W malayı* (Brug 19 7) Rao and Maplestone, 1940 *Onchocerca volvulus* (Leuckart, 1893) Raıllıet and Henry, 1910, *Loa loa* (Cobbold, 1864), Castellanı and Chalmers 1913, are ımportant pathogens for man Less ımportant specıes ınfect

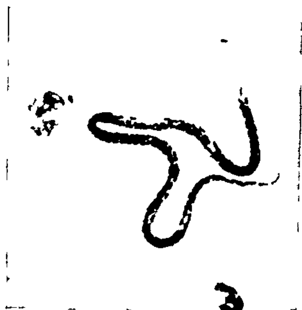


Fıg 15 *Mansonella ozzardı* Mıcrofilarıa x 840 Note long poınted taıl and absence of sheath (Orıgınal photomıcrograph from staıned blood film receıved from Dr Harry Schwachman)

ıng man ınclude *Mansonella ozzardı* (Manson, 1897), Faust 19 9, *Acanthocheılonema perstans* (Manson, 1891), Raıllıet, Henry and Langeron 1912 and a number of forms known only ın the mıcrofilarıal stage

These later named specıes whıle of questıonable pathogenıcıty, must be consıdered ın establıshıng a specıfic dıagnosıs, and a knowledge of theır geographıc dıstrıbutıon and characterıstıcs of theır mıcrofilarae ıs therefore essentıal

Mansonella ozaardı ıs lımıted geographıcally to Central Amerıca, the northern countrıes of South Amerıca, the northern states of Argentına and probably occurs ın most of the ıslands of the West Indıes Lıke

all other filariases the distribution is discontinuous and spotted within the endemic countries The incidence of infection likewise is variable but in some native villages over 50 per cent of the inhabitants have been found positive upon blood examination Our knowledge of the adult worms is based largely on the studies of a few specimens obtained in 1902 at autopsy on a native of St Lucia Five specimens all female were found in the connective tissue of the mesentery They varied from

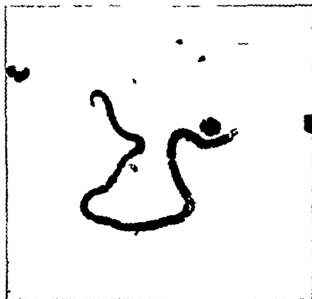


Fig 16 *Acanthocheilonema perstans* Microfilaria x 840 Note blunt rounded tail and absence of sheath (Original photomicrograph from stained blood film received from Dr Harry Schwachman)

65 mm to 81 mm in length and from 0 21 to 0 ; mm in breadth The microfilariae are very small usually not more than 200μ long and 5μ in breadth (Fig 15) They show no periodicity in the peripheral blood they are exceedingly active in fresh blood films and in stained films they assume outlines of small bow knots They are unsheathed and have a sharply pointed tail free of nuclei a character which early suggested the common name the sharp tailed filaria of British Guiana Development of the microfilaria is completed in the midge *Culicoides furens* which insect is believed to be the usual vector

Acanthocheilonema perstans, except for its apparent absence in the Greater Antilles, has a geographic distribution in the Western Hemisphere similar to that of *Mansonella ozzardi*. In some localities it has been known to be characteristically limited to coastal areas, whereas *M. ozzardi* may extend inward along river valleys. *A. perstans* in the Americas is probably of African origin, where its incidence is high throughout west coastal countries and the Congo Basin.

The parental worms occur in the connective tissue of the mesentery, perirenal and retroperitoneal tissues, the pericardium and occasionally in subcutaneous cysts. The microfilariae are unsheathed and nonperiodic. They are practically identical in size with the microfilariae of *Mansonella ozzardi* but can be identified readily in stained films by the bluntly rounded caudal extremity containing prominent nuclei to its tip (Fig. 16). In Africa the midge *Culicoides austeni*, is a known vector of *A. perstans*. Its vector in the Americas has not been identified.

The established species of filarial parasites were, as a rule, first discovered and known for some time only in the microfilarial stage. They were temporarily placed in the genus *Microfilaria* Cobbold, 1880, a collective group name created to contain immature *Filarioidea* not developed to a stage which permits a determination of the genus. The species still remaining in this category are, for the most part, poorly known and are of doubtful taxonomic position, but of these, *M. streptocerca* (Macfie and Corson, 1922), Stiles and Hassall, 1926, appears to be valid.

Microfilaria streptocerca was first discovered in small pieces of skin of healthy natives of the Gold Coast, Africa, and later reported in natives in the Mamfe division of the Cameroons. About 50 per cent of the inhabitants in some villages have been found infected with *M. streptocerca*. This is an unsheathed microfilaria, and in stained preparations it averages 215 μ in length, and its greatest diameter is about 3 μ. It strikingly resembles a shepherd's staff with its crook at the caudal extremity (Fig. 17). In stained section of parasitized skin the microfilariae lie in the tissue spaces of the corium, usually close to the *rete mucosum*. They do not occur in the blood. It is not unusual for natives to show simultaneous infection with *M. streptocerca*, *Onchocerca volvulus* and *Acanthocheilonema perstans*. Very recently, Peel and Chardome[9] reported the finding of the parent worm (female) of *M. streptocerca* in chimpanzees in the Belgian Congo. Dubois and van den Berghe regard this form as a species of the genus *Acanthocheilonema*

Bancroftian Filariasis

The enormous enlargements of parts of the body, particularly of the legs and external genitals, so frequently accompanying bancroftian filariasis were noted and much studied long before the etiological agent Wuchereria bancrofti was discovered. According to Menon[1] the first and a very good description of these conditions was written about 600



Fig 17 *Microfilaria streptocerca* x420 Note crooked attitude of tail (Original photomicrograph from stained blood film received from Dr Louis van den Berghe)

B C by Sushruta in India The disease probably was known also at the time in Persia Arabia Egypt and parts of Africa Hillary gives a very good account of its ocurrence in Barbados describing the recurring attacks of fever the lymphangitis the lymphadenitis and the slowly increasing swelling of the affected part up to the stage at which typical elephantoid appearances become definite and prominent Hillary was certain that the disease had been brought to the West Indies from Africa by negro slaves and at his time was observed to be too frequent among them and among the white people also Neumann[33] estimated that in

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Bancroftian Filariasis

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Fig 1, *Microfilaria streptocerca* x4 o Note crooked attitude of tail (Original photomicrograph from stained blood film received from Dr Louis van den Berghe)

B C by Sushruta in India The disease probably was known also at the time in Persia Arabia Egypt and parts of Africa Hillary[2] gives a very good account of its ocurrence in Barbados describing the recurring attacks of fever the lymphangitis the lymphadenitis and the slowly increasing swelling of the affected part up to the stage at which typical elephantoid appearances become definite and prominent Hillary was certain that the disease had been brought to the West Indies from Africa by negro slaves and at his time was observed to be too frequent among them and among the white people also Neumann[3] estimated that in

1881 six per cent of the population of St Croix, Virgin Islands, had elephantiasis

Observations demonstrating the etiology of elephantiasis were initiated in 1863 by the French surgeon Demarquay, who found microfilariae in chylous urine of a person who had lived in Cuba, were continued by Lewis in India and culminated in the research of Patrick Manson in China between 1876 and 1900 Early in his investigations Manson discovered filarial periodicity and experimentally demonstrated that the mosquito, *Culex quinquefasciatus*, was an essential intermediate host and the common agent for dissemination of the parasite Later investigations were largely directed along epidemiological and pathological lines Keen interest in bancroftian filariasis developed during World War II following the report of its high frequency and its serious disabling effect in thousands of United States Navy personnel who were serving in the South Pacific areas

Geographical Distribution

Bancroftian filariasis is widespread in tropical and subtropical countries It characteristically occurs in island populations or along more or less broad low-lying coastal areas of the larger islands and continents Indigenous infections are seldom to be found in the foothills or beyond coastal plains

In Asia the parasite is established along the coastal areas from Arabia to the Shantung Province in Eastern China It is prevalent throughout the islands of the East China Sea, southern Japan, southern Korea and the Oceanic Islands In Australia its distribution is mainly limited to the Queensland coasts In Africa the infection is found in tropical east and west coastal areas lower Egypt, Madagascar and neighboring islands Contrary to apparently current conception it does not extend across tropical Africa i e it does not occur in the Central Congo areas and is rare in the Sudan In the Americas *W bancrofti* is very common along the northern coast of South America particularly the littoral of the Guianas and Venezuela, to a lesser extent along the northern coast of Colombia, east coastal Costa Rica, and it is generally prevalent throughout the West Indies

Although bancroftian filariasis is widespread throughout warm countries it is always a focal infection and is neither evenly distributed nor uniformly prevalent in any country

Within endemic areas it primarily occurs in urban populations It

is often restricted to a few towns or to sections of towns which are densely populated and poorly sanitated It is particularly common in overcrowded dwellings of poor people and the incidence and morbidity in a given family may be striking

The parental forms of *W bancrofti* are parasites of the lymphatic system of man only They may be found at any point in the lymphatic

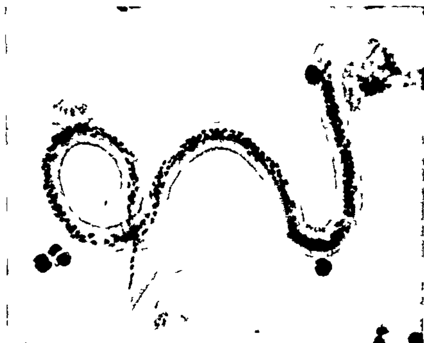


Fig 18 *Wuchereria bancrofti* Microfilaria x 840 The sheath extends some distance beyond the tip of the tail Note the smooth graceful curve of the body (Original photomicrograph from stained blood film received from the late Dr F W O Connor)

system but they ocur most frequently in the limbs scrotum and inguinal regions The two sexes are frequently coiled together in the periglandular tissues the afferent lymphatics and in the cortical sinuses In heavy infections they may occur also in the medullary sinuses They probably do not migrate from the site of their development The adult worms like other nematodes show marked sexual dimorphism The male worm measures about 40 mm in length and 0 1 mm in diameter, and the female is at least twice as large Further anatomical details of the

parental forms will not be recorded here, since the adult worms seldom enter in the diagnosis When their identification is desired, the specimens should be examined by a person well experienced in nematode morphology and taxonomy

The microfilariae occur in the lymph and the blood stream, and under certain conditions (chyluria) may be found in the urine In fresh preparations under low power of the microscope they appear as exceedingly active, thread-like objects as they lash their way among the blood corpuscles They vary from 250 to 300 µ in length and from 7 to 10 µ in breadth They are covered with a hyaline sheath which may extend some distance beyond the anterior and posterior limits of the body (Fig 18)

In stained blood films the microfilariae assume a smooth, graceful curve The head is rounded The body of the microfilariae is mainly composed of small nuclei A clear space, the nerve ring, is present at a point about one fifth of the length of the body backward from the anterior end Another break in continuity of the nuclei occurs at about the junction of the upper third and the lower two-thirds of the body This second clear area is known as the "anterior V-spot" or excretory pore A smaller spot is visible a short distance from the end of the tail which is known as the posterior V-spot", which represents the anal opening The nuclei do not extend into the tip of the head or into the tip of the tail

In most endemic areas the microfilariae characteristically exhibit a marked nocturnal periodicity They are found in greatest number between ten o'clock in the evening and two o clock in the morning but during the day usually few, if any, microfilariae are readily demonstrable in the peripheral blood (Fig 19) We have no adequate explanation for this remarkable phenomenon In most areas of the Philippine Islands however and on some of the South Pacific Islands, namely, Tahiti the Tonga Fiji, Samoan Wallis and Ellice Islands the microfilariae show no periodicity and remain in about equal numbers at all hours of night and day

For further development and dissemination of the parasite the circulating microfilariae must be ingested by suitable mosquitoes the sole vectors of bancroftian filariasis The factors, which determine the suitability of particular mosquitoes are not known Development takes place readily in mosquitoes of a variety of genera including *Culex*, *Aedes* and *Anopheles*, but closely related species within these genera differ widely in their ability to serve as hosts

Metamorphosis of the microfilariae and their development into the infective stage for man occur in the thoracic muscles of mosquitoes Under highly favorable conditions the infective stage is reached after about ten days It travels through the thoracic muscles into the anterior part of the labium (the sheath which encloses the biting mouth parts) where it awaits an opportunity to get back to man which opportunity is presented when the mosquito again feeds upon man Unlike the

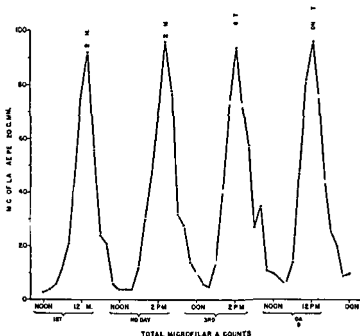


Fig 19 Bancroftian filariasis Microfilarial periodicity chart (After Low and Manson Bahr)

development of the malaria organisms in the mosquito there is no multiplication of filaria larvae within the body of its vector The transmission of bancroftian filariasis is accomplished with much less certainty than that of malaria

When the mosquito feeds upon a person the infected larvae escape from the distal portion of the labium of the mosquito and momentarily become free on the skin They then actively enter the human host by penetrating the moist skin entering presumably through the wound made by the mosquito or through a breach in the skin

Nothing is known about the larvae, after they enter the human host, until they appear as adult worms in the lymphatic system. Judging from observations on a related species, *Dirofilaria immitis*, in the dog the development of *W. bancrofti* to functional sexual maturity probably requires at least several months. For production of microfilariae it is necessary that the worms of opposite sex come to lodge and develop together in the same spot. Successful infections, therefore, probably are in most cases the result of mass biting by infected mosquitoes.

Pathology

Despite positive statements in the literature, the host-parasite relationships in bancroftian filariasis remain largely an assemblage of ideas and lack of experimental proof. Experimental proof, however, is difficult because man is the only vertebrate host of *W. Bancrofti*, and no similar histological changes have been associated with any known filarial species infecting lower mammals.

The disorders in bancroftian filariasis usually are attributed to interference with the lymphatic system. It is generally held that living microfilariae are not particularly pathogenic. Living microfilariae readily pass unharmed through normal lymph nodes. They are exceedingly active in the blood stream and they apparently never make permanent plugs in the vessels or form emboli. However, in view of the fact that some, probably many, of the infective larvae, which may gain entrance into the host, may be destroyed before reaching maturity, and that hundreds of thousands of microfilariae are being destroyed constantly within the body, it is entirely possible that at least some of the manifestations of bancroftian filariasis in some individuals are allergic responses.[4]

Early in the study of bancroftian filariasis it was believed that, in addition to the presence of the worm itself, traumatism or some other cause was needed to provoke lymph stasis and lymphangitis. The British Filariasis Commission in 1924 went so far as to say that the worms, per se, produce no symptoms, and that all the pathological manifestations associated with filariasis are due to secondary infections by pyogenic bacteria. To French scientists Montestruc and Bertrand[6] and Chabeuf[7] the parasite plays a more or less accidental role in the production of tropical lymphangitis or lymphatic filariasis. Grace[8] holds that tropical lymphangitis is produced by a combination of lymph

stasis caused by the parasite and subsequent infection by beta hemolytic streptococcus. Dickson and associates[9] Zuckermann and Hibbard[60] and other workers having studied filariasis cases among U S Navy personnel who served in the South Pacific areas urge a return to the orthodox opinion of the direct responsibility of the worm for the manifestations of bancroftian filariasis but the evidence on which bacterial infection is ruled out is not convincing[51,6]. At the present time it

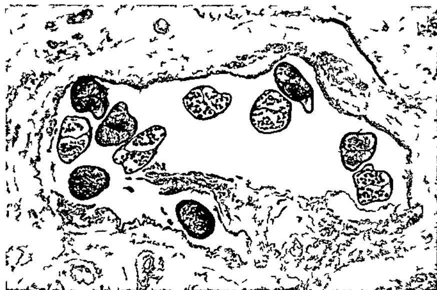


Fig. 20. Bancroftian filariasis. Sections of living female worm in dilated lymphatic vessel near the rete testis. There is no inflammation, obstruction or hypertrophy of the vessel. (Original photomicrograph of material received from the late Dr. F. W. O'Connor.)

would appear that most authors lean toward the view that the maturing and adult parasites and their secretions are responsible for the inflammatory reactions of bancroftian filariasis particularly in the early stages. Some of the more serious later complications obviously are due to secondary infection.

In most cases of bancroftian filariasis the living worms cause little or no damage other than varying degrees of blockage of afferent vessels of the lymph node[63,64]. Their presence early causes simple dilatations of the vessel (Fig. 20). Occlusion of the vessel may follow due to an accumulation of epithelioid cells and lymphocytes within the lumen and

its subsequent narrowing and obliteration by granulomatous perilymph angitis Severe inflammatory reactions, giant cell formation and massive fibrosis are prominent in the environment of dead and dying worms the reaction becoming more marked with advancing disintegration and calcification of the parasites (Fig 21) In heavy and long standing infections extensive areas may be involved resulting in complete obstruction of lymph drainage to a part with development of lymphedema and elephantiasis, due to subsequent extensive fibrous overgrowth This

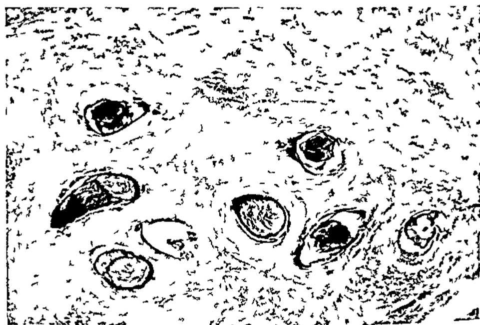


Fig 21 Bancroftian filariasis Sections of a disintegrating and calcified female worm in an inguinal lymph node The vessel is completely obliterated following extensive fibrotic changes (Original photomicrograph of material received from the late Dr F W O Connor)

sequence of events has been produced under experimental conditions by Drinker and Homans[6]

Eosinophilic leukocytes may be rare or absent about living worms but characteristically occur in enormous numbers in the vicinity of dead and disintegrating parasites In the early stages of disease neutrophilic leukocytes may be absent from the cell picture, thus indicating that the inflammation at this time is not necessarily caused by bacterial infection

The skin of elephantoid tissue in bancroftian filariasis is characteristically dense and leathery and because of destruction of the sweat

glands is dry It may be smooth and glossy but frequently it is rough warty and even nodular Folds appear, and deep abscesses frequently develop following abrasion and bacterial or mycotic infection

In the absence of demonstrable parasitism the pathology in bancroftian filariasis is essentially the same as in sporadic cases of lymph adenopathy and elephantiasis in which filariasis is not a factor Elephantiasis grossly identical with bancroftian filariasis is common among natives of inland tropical Africa areas where *Wuchereria bancrofti* is

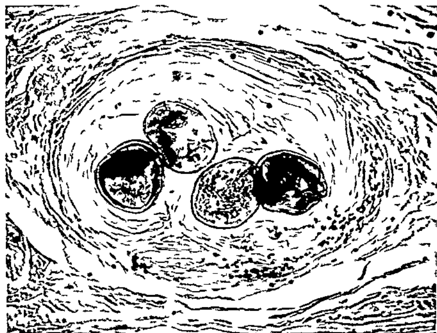


Fig 2 Bancroftian filariasis Four sections of a calcified worm in a subcutaneous lymph vessel a focal spot Inflammation has subsided the vessel is occluded Note the formation of concentric rings of fibrous tissue (Original photomicrograph of material received from the late Dr F W O Connor)

rare or absent To what extent this type of endemic elephantiasis resembles endemic bancroftian elephantiasis is not known

Symptomatology

The symptoms of bancroftian filariasis can be divided into inflammatory and obstructive The effects of inflammation are the first to

appear, and these may include lymphedema, lymphangitis, lymphadenitis funiculitis epididymitis, orchitis, filarial fever, myositis and abscess Obstructive phenomena are the result of progressive inflammatory reactions They include lymph varix, chyluria, hydrocele and elephantiasis

The early signs and symptoms of bancroftian filariasis are both vague and variable, but attacks of lymphedema, lymphadenitis and lymphangitis of one form or another, are at present considered cardinal signs of the disease in endemic areas The initial attacks may appear without warning and without apparent cause, but sometimes they develop following unusual exertion or exposure Lymphangitis in bancroftian filariasis appears to be characteristically retrograde The local symptoms usually are associated with varying degrees of generalized malaise, pain, numbness fatigue and slight rise of temperature ("filarial fever") At the height of a severe attack the entire arm or leg may become red, tender and painful, but within the affected extremity there may be one or more areas, "focal spots", where the pain is especially severe Both living and degenerate parasites have been found in biopsy material removed from such areas (Fig 22) The initial attacks usually cease spontaneously after a few days but tend to recur after shorter or longer intervals Symptoms of bancroftian filariasis in foreign residents may be complicated by psychic trauma, particularly fear of impotence or sterility[66]

In the obstructive phase of bancroftian filariasis lymphatic dilatation without rupture leads to lymph varix Lymph varices or varicose glands commonly occur in the skin particularly on the abdomen, legs or arms, in the groin, in the scrotum, the spermatic cord and in the abdominal lymphatics around the kidneys and those of the bladder wall Hydrocele commonly occurs in bancroftian filariasis When not complicated by infection, the hydrocele fluid is clear, straw-colored and may contain microfilariae Lymph varices frequently develop spontaneously without local or general symptoms and may become marked without the patient being conscious of them Chyluria frequently develops upon rupture and drainage of a lymph varix into bladder or kidney pelvis Here again the onset usually is abrupt, often without warning but frequently preceded by pain or aching in the kidney region The urine may be chylous at one time but clear at another, depending on temporary closure of the ruptured lymphatic

Elephantiasis is the most striking phase of bancroftian filariasis (Figs 23 and 24) The scrotum and legs are involved more frequently the arms, penis breasts and vulva less frequently Elephantiasis usually

develops only after repeated attacks of lymphangitis The process usually is slow, but in some cases enormous enlargements have developed within a few years

The blood picture usually is not altered in bancroftian filariasis Eosinophilia frequently is present but probably in most instances is related to concomitant helminth infection



Fig 3 Elephantiasis of the legs attributed to bancroftian filariasis of 45 years duration in a patient 70 years old British Guinea (Photograph by Dr T H Weller)

Diagnosis

The absolute diagnosis of bancroftian filariasis usually is made on finding the characteristic microfilariae in the blood (Fig 18) When obtaining blood for examination the phenomenon of periodicity should be considered Both day and night specimens should be collected (Fig 19) It should be remembered also that microfilariae may not be present in the peripheral blood of many cases showing suggestive signs and symptoms in both early and advanced phases of infection and that

therefore, negative findings do not necessarily rule out the diagnosis of filariasis Conversely, the presence of microfilariae does not necessarily imply filarial disease

For the examination of blood for microfilariae six or eight large

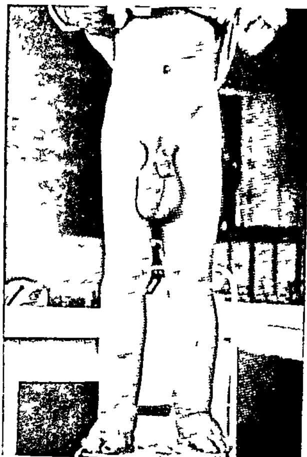


Fig 4 Elephantiasis of the legs and scrotum attributed to bancroftian filariasis (Photograph from Romiti)

drops of blood are allowed to fall from the tip of the finger on to an ordinary clean slide and evenly spread before clotting over the surface of the slide The blood films are dried in a level position, protected from insects and dust but freely exposed to the air They are then dehemoglobinized in water When laking of the hemoglobin is complete the slides are examined while still wet under a low power of the microscope The microfilariae if present, appear as glistening objects and are readily distinguishable

For morphological study and identification of the microfilariae the dehemoglobinized preparations may be stained with steaming Delafield's hematoxylin for 5 minutes and then washed with tap water They should then be differentiated momentarily in acid alcohol washed again in tap water until blue dehydrated in absolute alcohol cleared in xylol and mounted in Canada balsam clarite x (thermoplastic hydrocarbon resin) or any other satisfactory mounting medium

If the above method fails to reveal infection further search for microfilariae should be made by using a method which will concentrate them For such examination about 10 ml of venous blood should be withdrawn, laked and centrifugalized at 2,000 revolutions per minute The sediment then is transferred to a few drops of normal saline on a glass slide for immediate microscopic examination The microfilariae usually regain activity in the saline The concentration method should be used in the examination of chylous urine for microfilariae

Search for adult parasites in biopsy material is not recommended as a routine diagnostic procedure Adult worms usually are found in not more than 30 per cent of the cases The histopathological changes within the node are suggestive but not specific for bancroftian filariasis The finding of these changes usually has been considered confirmatory *of the diagnosis in persons known to have been exposed to infection and* in whom clinical symptoms are present but actually it calls for further careful search for the worm in the excised material and for further search for microfilariae in the blood

Frequently the diagnosis is made upon the presence of certain symptoms when they are noted in natives or foreign residents in endemic areas These symptoms usually are referable to the early stages and include lymphangitis lymphadema lymphadenopathy myositis and sometimes abscess There is however considerable disagreement among authorities on just what should be included under signs and symptoms of bancroftian filariasis. Lymphangitis lymphadenitis lymph edema and particularly permanent enlargement of the epitrochlear lymph node are considered by Buxton[67] and others to be the earliest positive signs of the disease Iyengar[68] however excludes the presence of enlarged lymph nodes lymphadenitis and abscess because he could not determine to what extent they represented filarial disease but includes elephantiasis lymph scrotum hydrocele and lymphangitis particularly retrograde lymphangitis *Buxton recorded hardness or enlargement of* the testicle and epididymis and the presence of hydrocele as manifestations of bancroftian filariasis but finding it difficult to define a boundary

between a normal testicle and epididymis and one that was enlarged or fibroid, he concluded that the male genitalia do not provide useful physical signs in the diagnosis of filariasis Recently Webster[69], from a study of case histories of 80 adult white persons with an average duration of residence of 26 years in the Samoan Islands and showing signs and symptoms of bancroftian filariasis, concluded that the mere presence of palpable axillary inguinal or epitrochlear lymph nodes is of little value in the diagnosis in areas where bacterial infections of extremities are extremely common

During World War II 10,421 United States cases of bancroftian filariasis were reported among U S Navy personnel following service in the South Pacific area particularly in the Samoan Islands[0] The diagnosis in most of these cases was based upon (a) the presence of a transient retrograde lymphangitis localized lymphedema or lymphadenitis, (b) service leading the exposure to infection and (c) a positive reaction to an intradermal test

To evaluate the importance of lymphadenitis in filariasis a careful physical examination with particular reference to the presence of palpable lymph nodes was made on 200 men of the above group with a clinical diagnosis of bancroftian filariasis -71 cases of malaria and on 98 men who had not been in tropical areas The data obtained from this study showed no significant differences either in the number of men with demonstrable adenopathy or in the average number of nodes in any particular area Patients in the overseas groups had larger nodes than those in the control groups, which differences could be accounted for by the existence of active fungous infections in the overseas group Although lymphadenitis usually is considered to be the most frequent clinical manifestation of bancroftian filariasis, in the above study it could not be used as a diagnostic criterion

There is close agreement among the authors that lymph varix, chyluria and elephantiasis usually are indicative of bancroftian filariasis in the later stages when occurring in natives and foreigners having had a prolonged residence in an endemic area

Various skin tests have been employed in the diagnosis of filarial infection The number of positive intradermal responses following the use of non-specific antigens in suspected cases of filariasis led to the conclusion that this test was of diagnostic value Results of later applications of these tests however gave irregular and uncertain results False positive reactions are believed due to cross sensitivity i e a helminth group reacting factor from nematode infections other than filarial

worms[17] and probably to immune responses produced by infective filaria larvae of non human filarial species[2] Unfortunately immunological tests at present cannot be relied upon for final decision in the diagnosis of filariasis

The only way of making a positive diagnosis of bancroftian filariasis is by identification of the infecting parasite either adult worms or microfilariae The recognition and correct diagnosis of this disease in the absence of demonstration of the parasite usually is difficult and requires detailed study Lymphadenopathy lymphedema and lymphangitis always should suggest the possibility of bancroftian filariasis when occurring in persons living or having lived in endemic countries Of these the commonest and most characteristic initial manifestation of the disease appears to be an acute transient retrograde lymphangitis.

Treatment

There is no accepted chemotherapy for bancroftian filariasis At the present time the antimony compounds neostibosan[13] and anthiomaline[14] and a phenylarsenoxide hold promise but still remain in the experimental stage Their action on the parasite is slow requiring months for complete disappearance of microfilariae from the blood The toxicity of these compounds must be further investigated before they can be recommended for general use

More recently Santiago Stevenson and associates[8] reported highly favorable results including rapid disappearance of microfilariae from the blood stream following oral administration of 1 diethylcarbamyl 4 methylpiperazine hydrochloride (hetrazan) The drug was administered orally 3 times daily before or after meals or every 8 hours The individual dose varied from 0 5 mgm to 2 mgm per kilogram of body weight and the number of days during which treatment was given varied from 3 to 21 days The drug is reported to have been well tolerated in all of the 26 cases treated

Palliative measures with elevation of the affected part usually are recommended for the immediate treatment of acute inflammatory attacks, but Glauser[7] and Coggeshall[16] did not find heat cold massage or infra red rays beneficial to affected parts Rest usually affords relief Following removal of the patient afflicted with early filariasis from the endemic area to favorable surroundings the disease soon runs a self limited course before actual evidence of parasitism can be demonstrated

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icity but do not disappear entirely from the peripheral blood during the daytime They resemble bancroftian microfilariae but are identified by the presence of two distinct nuclei in the tip of the tail (Fig -5) Mosquitoes of the genus *Mansonia* are the principal vectors particularly *M* (*Mansonioides*) *annulifera* These mosquitoes are nocturnal feeders and are most active during the evening from 7 to 9 o clock

A floating plant *Pistia stratiotes*, is essential for the breeding of

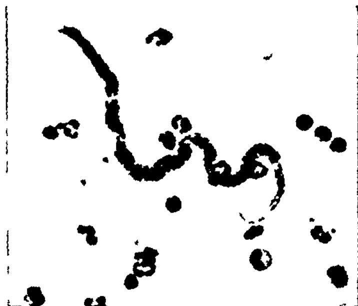


Fig 25 *Wuchereria malayi* Microfilaria x 840 (Original photomicrograph from stained blood film received from the late Dr Candido Africa)

Mansonia The female mosquito does not ordinarily lay eggs except on the leaves of *Pistia*, and the larvae being structurally adapted to obtain their supply of oxygen from the air cavities in the root of the plant are not capable of living apart from it In experimental areas the clearance of ponds and tanks of *Pistia* markedly reduce the incidence of *Mansonia* mosquitoes and checked further spread of the infection[13]

ONCHOCERCIASIS

Onchocerciasis in man is caused by *Onchocerca volvulus* (Leuckart 1893) Railliet and Henry 1910 the adult forms of which are charac

Bancroftian filariasis is seldom fatal. Sulfonamide drugs are recommended in the treatment of filarial lymphangitis complicated by streptococcal or staphylococcal infection. Pressure bandages are recommended in early elephantiasis of the legs. The bandaged leg must be exercised to prevent cyanosis. The large fibrotic tissues of advanced elephantiasis frequently have been removed successfully by surgery[..]

Prevention and Control

In view of the fact that the parasite is transmitted solely through the bites of mosquitoes, its prevention is primarily one of mosquito control. *Culex quinquefasciatus* probably is the commonest vector of bancroftian filariasis. It is essentially a domestic mosquito and worldwide in its distribution. Other important vectors are *Aedes scutellaris pseudoscutellaris* in the Oceanic Islands and *Anopheles annctus* in Australia.

Factors which favor endemicity of bancroftian filariasis are known to vary greatly not only in different countries but also in different nearby localities within an endemic country. Thorough analysis and understanding of these factors are essential before effective control can be realized. The identity of the mosquito vector and knowledge of the conditions, which permit it to flourish, are of first importance in control of the disease in mankind. Better housing conditions, screening of doors and windows and the use of bed nets are often recommended but such measures, although effective if properly carried out, are seldom applicable to native populations. At the present time the only effective measures against bancroftian filariasis are those which can be applied directly against the mosquito vector.

Brug's Filariasis

Brug's filariasis, caused by *Wuchereria malayi*, appears to be strictly oriental in geographical distribution. It is known to occur in the Federated Malay States, Sumatra, Java, Ceylon, parts of India, Indo-China and in north eastern Chekian Province of China. It is often the dominant species of a given region and, whereas *W. bancrofti* characteristically occurs in villages and towns, *W. malayi* occurs typically in rural districts along river or forest settlements. Elephantiasis of the feet and legs is associated characteristically with *W. malayi* infection, the genitals and upper extremities are rarely involved. The microfilariae show nocturnal period

been obtained with hetrazan' (1 diethylcarbamyl 4 methylpiperazine hydrochloride) in onchocerciasis by Mazzotti[9] in Mexico

Onchocerciasis is very common along the west coast of Africa from Sierra Leone to the Congo basin and extending eastward through the Congo into Uganda Anglo-Egyption Sudan and Kenya It also oc

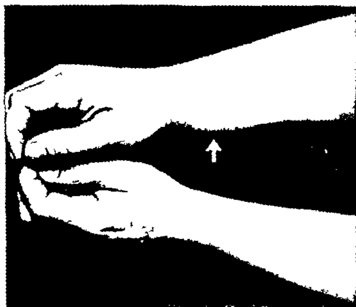


Fig Loiasis Calabar swelling in a female missionary (Photograph from Guy Cohen and Jacob)

curs endemically in southern Mexico and Guatemala upon the Pacific or southern slopes of the volcanic ranges at altitudes betwe n 2000 and 4500 feet

Black flies (*Simulium damnosum S neavei*) are particularly concerned in the transmission of onchocerciasis in Africa *S metallicum S callidum* and *S ochraceum* are the vectors in endemic regions of Mexico and Guatemala[10] The development of the parasite in these flies and its transmission to man are essentially the same as the development and transmission of *Wuchereria bancrofti* in and by mosquitoes

Loiasis

Loiasis is a form of filariasis caused by *Loa loa* (Cobbold 1864) Castellani and Chalmers 1913 The infection frequently is associated with

teristically found in prominent, subcutaneous, fibromatous tumors The microfilariae appear in large numbers in the skin especially in the vicinity of the tumor, in the eyes, the conjunctivae and the cornea and in the central portion of the tumor with the adult worms They do not appear in the circulation but may occur rarely in the deeper tissues and viscera When seen in fresh sections of the epidermis or conjunctiva, they are actively motile and possess no sheath (Fig 26) Two sizes are clearly distinguished, suggesting a sex difference



Fig 6 *Onchocerca volvulus* Microfilariae x420 (Original photomicrograph from stained biopsy material received from Dr David Weinman)

It is believed that the tumor results from the irritation produced by the presence of the adult worms and the products of their metabolism Unencapsulated adult worms have been noted The microfilariae have been considered to be a cause of an erysipelatous condition of the face and head and of disturbances in vision iritis, punctate keratitis and total blindness[30]

Van Hoof and associates[31] recently observed destruction of the parasites, resorption of the tumors and amelioration of symptoms following treatment with Bayer 205 The drug, however produced unfavorable reactions in some cases and further studies are needed before its use in onchocerciasis can be recommended Encouraging results have

sheathed forms In stained films they appear somewhat stiff and angular whereas microfilariae of *W bancrofti* assume more sweeping and graceful curves (Fig 8)

L oa loa is transmitted to man by mangrove flies *Chrysops dimidiata* and *C silacea* The development of the parasite in these hosts is similar to that of other filarid worms

Development of the worm in man is slow It has been estimated that the life span of the adult worm is about 15 years Calabar swellings (Fig 7) which are generally regarded as allergic responses may reappear for years in the absence of other evidence of loiasis Aside from the itching and irritation caused by migrations of the adult worms and the transient subcutaneous swellings apparently no damage is done and the patient usually enjoys good general health[83] There is no effective chemotherapy known The adult parasites may be readily extracted through a small incision when they appear in the conjunctiva

Dracunculiasis

Dracunculiasis or dracontiasis is an infection of the connective tissues by *Dracunculus medinensis* (Linn 1758) Gallandant 1773

The female form of *Dracunculus medinensis* has been known through the ages as a dangerous parasite of man It is commonly referred to in the literature as the guinea worm Medina worm and the dragon worm and by some authorities it is held to have been the fiery serpent which troubled the ancient Israelites by the Red Sea

The adult female is unusually long and may attain a total length of over 1 meter although the average is perhaps not over 60 cm with a diameter of about 1 5 mm A cuticular shield or helmet is present at the anterior end The cuticle is smooth and presents a milky white appearance The alimentary tract below the esophagus is atrophied and is largely replaced by the long uterus which is filled with motile larvae The vulva is situated immediately behind the cephalic shield and during parturition the uterus is prolapsed through this opening

The male worm remained practically unknown until Moorthy and Sweet[84] obtained specimens from experimental dogs The specimens were recovered from the region of the esophagus beneath the right scapula the right orbit the meninges scalp the thoracic and abdominal walls and from the extremities The males are from 12 mm to 29 mm. long by 0 4 mm in diameter

The female worm when about to produce her young migrates

acute inflammatory responses and transient edematous swellings in various parts of the body, known as "calabar swellings" (Fig 27)

Loa loa is indigenous only in tropical West Africa and along the Congo River and its tributaries. It is noted occasionally in other countries among Europeans and Americans, particularly missionaries who have lived for some time in the endemic areas. The parental worms are parasites of the subcutaneous tissues, particularly of the arms, legs and head, and have been found in the peritoneum. When fully mature, they



Fig 28 *Loa loa* Microfilaria x 420 Sheath extends beyond both extremities of the body. Note angular irregular curves of the body

characteristically migrate and frequently appear beneath the skin in various parts of the body. Because of this habit they have been observed more often than any other adult filarial species infecting mankind. The male worm measures from 25 mm to 35 mm in length and about 0.35 mm in breadth. The female varies considerably in length up to 70 mm and is about 0.5 mm in breadth. The average length is about 50 mm. The cuticle is embossed with wart-like projections except at the anterior extremities of both sexes and at the tail of the male, which areas are smooth. The microfilariae show diurnal periodicity, appearing in the morning and disappearing at about 9 o'clock in the evening. They are

Symptoms

Urticaria, cyanosis dyspnea vomiting and diarrhea are noted at the time the female worm establishes connection with the surface of the body These symptoms are probably of an anaphylactic nature Usually the parasite may be innocuous if not interfered with Should the worm break through accident and the larvae become discharged into the tissue, violent inflammation and fever followed by abscess formation and sloughing may develop and result in death from septicemia Sterile abscesses may arise should the worm fail to reach the surface of the skin The failure to absorb such dead parasites may give rise later to the formation of dense fibrous bands which may become calcified and persist for years as hard, twisted cords beneath the skin

Diagnosis

Diagnosis usually is made at the time the female worm appears in the cutaneous tissues However a patient with a bulbous vesicle or sinuses on the feet or legs in an endemic area is almost certainly suffering from dracunculiasis (Fig 29) Calcified forms may be detected by x ray examination The prognosis usually is good

Treatment

It has long been the custom to extract the worm by gradually rolling it on a small stick A few turns are given the stick each day until the worm is entirely drawn out This method is dangerous however because the worm frequently breaks while still within the tissue and this may be followed by severe inflammation and conditions previously mentioned Frequent douching of the ulcer and the part occupied by the worm with cold water hastens the complete expulsion of the larvae after which the worm may emerge spontaneously or may be extracted without resistance Elliott[85] obtained very satisfactory results in the treatment of dracontiasis by injecting hot olive oil emulsions of phenothiazine into the vicinity of the worm The drug kills the worm usually in about seven days If the worm is visible it is then extracted

Epidemiology

Dracunculiasis is highly endemic in tropical Africa and western India It occurs also in Arabia Russian Turkestan Afghanistan and Iran It is reported to be endemic in the state of Bahia Brazil In countries

to the parts of the skin which are likely to, or frequently do, come in contact with water such as the arms and legs or the backs and shoulders of water carriers A small vesicle soon appears and ulceration follows (Fig 29) A small hole may be seen at the base of the ulcer from which



Fig 29 Dracunculiasis Formation of a vesicle on the ankle prior to the appearance of the anterior end of the female worm end parturition (Photograph by Moorthy)

a portion of the anterior end of the worm may protrude When the affected parts come in contact with water a milky fluid is discharged directly from the hole in the ulcer or from the vulva, if the worm is exposed to that extent This fluid contains thousands of motile larvae which may swim actively about in the water The larvae are at first from 60μ to 750μ in length by 17μ in breadth and are characteristically flattened forms with a long slender tail well adapted for swimming

They are readily ingested by several species of *Cyclops* Shortly after ingestion the young worms penetrate the wall of the stomach and pass into the body cavity Within the body cavity of *Cyclops* the larvae undergo two molts acquire a cylindrical shape and in from four to six weeks become infective for man Infection in susceptible hosts results from swallowing infected *Cyclops* in drinking water The complete development of the worm in man is exceedingly slow, and it is not until the worm is about a year old that it seeks the surface of the body to discharge the young

name *Trichina* had been applied previously to a different animal, an insect. Railliet later coined the new word *Trichinella*, the genus in which the parasite now remains. Since the parasite is an animal, the choice of the non-committal terminative—*iasis*, signifying "disease of", is to be preferred to—*osis*, which generally infers an infection by a plant parasite. The term trichinelliasis therefore correctly designates the disease. However, the name trichinosis has been in constant usage since 1866[87] and is still preferred by the majority of American and European authors.

The infective stage of the parasite occurs only in the skeletal muscles of carnivorous or omnivorous animals. It is a somewhat advanced larval form of about 1 mm in length, about 0.035 mm in diameter, and is coiled in a corkscrew manner within a lemon-shaped capsule (host adventitia) which measures about 0.5 mm in length by 0.25 mm in breadth. Infected meat ingested by a susceptible host is first digested in the stomach, resulting in the freeing of the larval worms from their capsules. These larval worms pass directly into the small intestine where within the following days they become sexually differentiated adult worms. The females measure 3 mm to 4 mm in length and the males are about half the size of the females. Copulation may occur within the following days after ingestion and has been observed as late as the 13th day. The fertilized females separate from the males and burrow into the mucosa, and being ovoviviparous, the brood (minute larval worms approximately 0.1 mm in length) is deposited directly into the central lacteals of the villi or in other lymphatics. From the intestinal lymphatics these larvae pass through the regional lymph nodes into the thoracic duct and eventually to the peripheral blood circulation by which they are carried to all parts of the body. In experimental animals these migrating larvae may appear in the blood about 1 week after infection. They are most numerous in the blood between the 15th and 20th days and few, if any, are in the blood after the 28th day. From a review of the literature it would appear that the earliest that these larvae have been found in the blood in human cases is about the 15th day after infection.

Larvae which are carried to the skeletal muscles leave the capillaries and quickly penetrate the sarcolemma for further development within the muscle fibers. About 3 weeks after infection a larva will have obtained its maximum growth and it then assumes a spiral form. After 3 months a homogeneous hyaline oval capsule of collagenous fibrils is formed about the larva and within this protective covering it may remain viable and infective for several years. The cycle is repeated

where it is widespread, its distribution is characteristically discontinuous and important endemic centers often are separated by wide areas where it is not present It occurs in regions where there is low annual rainfall and at a time when the inhabitants are forced to depend for their drinking water on open pools, wells or cisterns in which *Cyclops* is abundant Infection, therefore appears to be seasonal, but the seasonal relation in dracunculiasis is explained by the fact that the development of the female worm takes about one year, and the yearly period of suffering from the disease coincides with conditions most favorable for its transmission, i e the end of dry season The greatest incidence of dracunculiasis occurs in villages with the poorest water supply

Natural infections with *D medinensis* have been reported from a large number of domesticated and wild animals including the dog horse cattle jackal wolf leopard monkey, deer, baboon, racoon, mink and fox The parasite has been reported in the silver fox from Iowa, the raccoon from New York and Ontario and the mink from Nebraska, but no indigenous infection has been observed in man in North America

Control

Since infection is always the result of swallowing water containing infected *Cyclops* boiling filtering or even straining the drinking water through a cloth would be effective in individual protection Permanent control can only be achieved by changing the water supply to eliminate sources of infection The introduction of draw wells use of chemicals in the drinking water and the introduction of fish (*Barbus* sp) which feed upon *Cyclops* have controlled dracunculiasis effectively in once heavily infected villages in India[86]

NEMATODE INFECTIONS AND DISEASES ACQUIRED THROUGH INGESTION OF FOOD

Trichinosis

Trichinosis or trichiniasis may be defined briefly as an acute disease produced by the invasion of the tissues and organs by larvae of a parasitic nematode *Trichinella spiralis* (Owen, 1835) Railliet 1896 Owen first gave the name *Trichina spiralis* to the parasitic nematode discovered in the muscles of a cadaver by his student, James Paget Because the generic

istic infection of temperate and cooler countries where its incidence is *in direct proportion to the extent to which raw garbage is fed to hogs* In the United States the incidence of trichinosis ranges from 3 5 to 36 0 per cent in different parts of the country with an average incidence of 16 1 per cent[89] It is estimated to occur in 5 7 per cent of our garbage fed hogs and in less than 1 per cent in hogs fed mainly on grain and forage It is exceedingly rare among native human populations of tropical countries

Symptomatology

There is no typical course in trichinosis The marked irregularity of the clinical course is understandable when it is realized that trichinosis is at one time in its course a blood stream infection and that the migrating larvae may lodge in other tissues besides the skeletal muscle in which tissues they are destroyed and absorbed The severity of the disease varies with the number of infective larvae invading the tissues and the physical condition of the patient In most cases trichinosis is a mild febrile disease The onset is variably reported from 24 hours to 40 days In the majority of cases the incubation period is 22 days or less frequently varying from 6 to 15 days Sudden appearance of facial edema of the upper eyelids is one of the commonest earliest and most characteristic symptoms in clinical trichinosis It is usually noted first on about the 11th day of infection and may be followed by subconjunctival and retinal hemorrhage conjunctivitis mydriasis pain and photophobia (Fig 30) Gastrointestinal symptoms acute diarrhea abdominal pain nausea vomiting and constipation may occur prior to or concurrent with ocular manifestations Gastrointestinal disturbances when present may not be followed by other symptoms

Fever muscle tenderness and pain especially on movement skin manifestations thirst, profuse sweating weakness and prostration anemia and rapidly ascending eosinophil count may follow shortly after the appearance of the ocular symptoms Muscle pain may be so severe that motion is restricted and reflexes are not obtainable These manifestations of which none is constant in time of appearance or severity are associated with the invasion and destruction of larvae in the tissues and injury and repair of the invaded tissues The fever usually is remittent and terminates by lysis It may begin from after the 10th to 20th day of infection usually reaches its peak several days to a week after its first appearance and may attain a a level of 104 F for a period

when meat containing viable larvae is ingested by a new host Encapsulated larvae are generally referred to as "trichinae"

Larvae, which fail to enter a muscle fiber, and those which fail to retain the protection of the sarcolemma, are surrounded by a focus of intense acute inflammatory reaction and are destroyed Such is also the fate of larvae lodging in smooth muscle and in the brain, heart, liver and other organs

The length of life of adult worms in the intestine varies with the host species and the intensity of infection, but it is seldom longer than from 4 to 5 weeks Following death the adult worms are digested and usually they are not found in the evacuated stool Similarly the productiveness of the female worms varies in different host animals It has been demonstrated with the guinea pig, a particularly susceptible host that 1,000 to 1,500 encapsulated larvae will generally develop from each female[88] The potential maximum number of larvae actually produced by one female would, for obvious reasons, be considerably greater

Trichinella spiralis has, perhaps a greater range of hosts than any other species of parasitic nematode It is likely that all mammals are more or less susceptible to infection Birds, particularly young chickens and pigeons, have been infected experimentally but muscle infection in these hosts is of short duration The most important hosts are man, the pig and the rat

Human trichinosis almost invariably has its source in infected pork Outbreaks of the disease have occurred in the United States from eating bear meat and cases developed during World War II in Germany following the eating of game and fur-bearing animals taken from zoological gardens Trichinosis in swine usually is the direct result of their eating raw trichinous pork either in garbage or in offal at the time of slaughter The primary source of rat trichinosis is like that for swine, raw, infected pork scraps in garbage collected for swine or in pork scraps picked up in the market districts or at abattoirs Contrary to current opinion rat trichinosis is transmitted rarely to swine Thus, human, porcine and rat trichinosis are all chiefly of porcine origin Outbreaks and epidemics of trichinosis in the United States frequently originate in home slaughtered hogs which have been raised on garbage collected from nearby cities Sporadic cases usually are attributed to infected pork and certain pork products purchased in standard markets Prenatal trichinosis may occur

Trichinosis has a world wide distribution It is, however, a character

cardium with production of necrotic and fragmented fibers Myocarditis is one of the most serious complications of trichinosis Death from myocarditis usually takes place between the 4th and 8th weeks

The presence of an eosinophilia particularly a rapidly ascending eosinophil count is probably the most constant and most characteristic symptom of trichinosis Eosinophilia usually begins during the 2nd week and may be delayed until 5 or 6 weeks after onset of illness It may be obscured or eliminated by a secondary bacterial infection and rapidly falls in fatal infections a few days before death"[9] The eosinophilia reaches its height in the 3rd to 4th week and then gradually

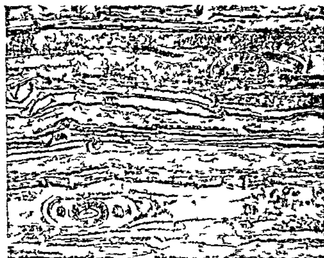


Fig 31 Active trichinosis human case Showing interstitial myositis and changes in skeletal muscle during the third to fourth week after infection

declines An eosinophilia of 87 per cent has been recorded The white blood cells may not be greatly increased but a hyperleucocytosis of 34 000 per cubic millimeter has been observed The blood chemistry in trichinosis is not significantly altered

Diagnosis

Trichinosis in epidemic form is likely to be correctly diagnosed The diagnosis of the sporadic and mildly ill cases may be difficult because of variable symptomology Symptoms which may develop during the intestinal stage of infection are non specific, and there are no diagnostic

of several days Patients may complain of chilliness Skin eruptions on the trunk, face and neck may develop, but these manifestations are relatively uncommon Subungual or "splinter" hemorrhages are recognized as a fairly common symptom in trichinosis[40] They occur along the distal ends of the nail beds and are of the nature of petechiae Respiratory symptoms may develop in the 3rd to 6th week due to migrating larvae in the lung capillaries and to their invasion of the respiratory muscles These symptoms may include, among others, persistent cough



Fig 30 Trichinosis Subconjunctival hemorrhages in two sisters of a family of eleven all suffering simultaneously from trichinosis and of which nine developed pronounced ocular manifestations

ing sore throat hoarseness, dyspnea pain within the chest and chest walls Hemoptysis may occur Pneumonia, an infrequent complication is most likely to develop from the 4th to 6th week after infection Delirium, particularly at night, may occur in the course of pneumonia

The destruction of larvae lodged in the central nervous system may give rise to neurological symptoms Headache is frequent and usually supra orbital in location Dizziness may be present, and not infrequently the mental attitude is one of apathy Insomnia, particularly in adults, may be distresssing but children are often drowsy and sleep well Deep reflexes may be lost Hemiplegia has been reported in a number of cases Cardiovascular complications result from the invasion of larvae in the myocardium Complete growth and encapsulation of larvae do not however take place in heart muscle The reaction in the heart is an active cellular infiltration usually focal, but distributed throughout the myo-

stupor and coma are of grave significance A sudden fall in the eosinophil count from a previously high level to 1 per cent or zero during the acute stage is an unfavorable prognostic sign Most deaths are due to myocardial failure and bronchopneumonia The mortality rate of clinically recognized trichinosis is from 5 to 6 per cent A sudden fall in the fever with restful sleep and the integrity of the cardio respiratory organs and central nervous system in the 4th or 5th week allows a good prognosis to be made The prognosis is generally favorable after the 8th week of infection Vague muscle pains and ready fatigue may be expected to persist for some months to a year after apparent recovery from trichinosis Repair of damage to the heart or tissue in which the parasite does not successfully develop is complete and probably never results in permanent disability[93]

Treatment

Despite the fact that trichinosis has been recognized since 1860 as a dangerous disease of mankind and search for an efficient therapeutic agent has been continuous none has as yet been discovered and treatment has been restricted to general supportive measures

In recent experimental infections hetrazan was found to destroy effectively adult intestinal worms when administered 24 hours after the infective feeding[94] but its action on migrating and muscle larvae appears to be of doubtful value

Prevention and Control

Federal inspection of meat does not guarantee freedom of pork or pork products from infection with trichinae Until drastic changes are made in the methods of garbage disposal throughout the country the only effective means of control is with the housekeeper which means that all pork must be cooked thoroughly before it is eaten

laboratory procedures Diarrhea, nausea, vomiting and other intestinal disturbances may be recalled by the patient later when under the care of the physician With incomplete clinical and laboratory data, trichinosis may be easily confused with acute nephritis, angioneurotic edema colitis, conjunctivitis, endocarditis, erysipelas food poisoning gastroenteritis, meningitis pelvic inflammatory disease, pneumonia, poliomyelitis, rheumatic fever, scarlet fever, syphilis, tuberculosis typhoid fever, undulant fever and upper respiratory tract infection[8] In all acute illnesses where there is a history of puffy eyelids in the patient or in a member of the immediate family or an edema of the eyelids at the time of physical examination, the diagnosis of trichinosis should be seriously considered

The most reliable laboratory procedure for the diagnosis of trichinosis is the daily study of blood, particularly of blood smears for eosinophilia Search for parasites in stool, blood spinal fluid and biopsy material (striated muscle) usually is futile Negative results do not rule out the diagnosis of trichinosis The presence of migrating larvae in incompletely developed capsules and myositis in striated muscle is absolute proof of active trichinosis (Fig 31)

Serological and skin tests have been widely used for more than 10 years in the diagnosis of trichinosis They show as high a degree of sensitivity as is found in any other clinical or laboratory procedure Limitations of these reactions should be kept in mind In view of the high incidence of trichinosis in the United States, it is to be expected that some patients will give positive reactions, even though their illness may not be related to acute trichinosis Negative results are more reliable in ruling out the diagnosis of trichinosis than positive tests are in establishing the diagnosis Briefly the diagnosis of trichinosis depends upon a careful history of the patient's illness a complete physical examination repeated examinations of blood films for eosinophilia and the use of skin and serological tests

Prognosis

The early accurrence of diarrhea is looked upon as a favorable prognostic sign In such cases it is likely that the patient has recovered from a previous trichinous infection which has sensitized the intestinal tract causing a rapid expulsion of the worms from the later exposure In children the prognosis appears to be generally better than in adults In cases complicated with pneumonia the outlook is poor Delirium

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CHAPTER XXXIX

DISEASES DUE TO CESTODES OR TAPEWORMS *

By E E Tyzzer and W G Smillie

Table of Contents

Introduction

The class Cestoda — tapeworms — are endoparasitic flat worms without an alimentary canal in general hermaphroditic and with few exceptions segmented in the adult state Typically are they composed of a head portion and a chain of segments each of the latter being equipped with sexual organs which

* Acknowledgment is made to Wm Wood and Co for the use of figures from Animal Parasites of Man by Fantham Stephens and Theobald and to John Wiley and Sons for the use of figures from Animal Parasites and Human Disease by Chandler

The segments are usually flattened and quadrilateral in outline but the lateral borders frequently bulge The ventral surface is recognized either by the presence of a uterine opening or in case this is not present it is determined by the position of the ovary which lies ventral to other structures The posterior border, that is that farthest from the scolex usually projects slightly over the somewhat constricted anterior border of the next succeeding segment The cuticle is represented by a homogeneous smooth or slightly wrinkled layer which for the most part, is devoid of spines or other appendages The young segment is composed chiefly of parenchyma which consists of elongated or branching cells lying in a non cellular matrix In the parenchyma of almost all species there occur refractive concentrically striated bodies containing carbonate of lime and known as calcareous corpuscles

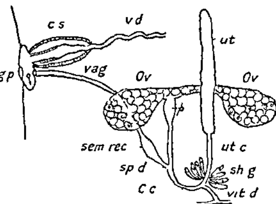


Fig 2 — Diagram of genitalia of a Cestode *gp* genital pore ♀ ♂ male and female ducts opening into genital sinus *cs* cirrus sac *vd* coiled vas deferens (outer seminal vesicle) *vag* vagina *sem rec* seminal receptacle *sp d* spermatic duct *Cc* fertilization canal *vit d* vitelline duct *sh g* shell gland *ut c* uterine canal *ut* uterus *Ov* ovary *p* pumping organ (After Stephens) ([illegible])

The musculature of the segments is composed of longitudinal transverse and dorso ventral fibers The longitudinal fibers are situated externally near the cuticle but the transverse or annular fibers occur in a dorsal and ventral layer and divide the matrix into cortical and medullary zones

The nervous system begins in the scolex and extends throughout the entire series of proglottides Several bundles of nerves are found extending longitudinally not far from the lateral borders *In the scolex these nerves anastomose to* form a complicated system or rostellar ring

The excretory system commences in flame cells similar to those found in trematodes (see chap XXXVII) scattered throughout the parenchyma These discharge into convoluted and anastomosing tubes which empty into the lateral vessels that extend along the lateral borders of the worm for its entire length *There are typically four such excretory canals but in many species two of these* are for the most part suppressed so that there is only one prominent canal near each border These longitudinal canals are commonly united in each segment by an anastomosing canal which crosses the segment near its posterior border

eventually become so greatly developed as to replace most other structures The head is structurally adapted for adhesion or fixation to the host The body is covered with cuticle the cells of which are imbedded in the parenchyma or supporting tissue The excretory vessels are symmetrical and open at the posterior end Nutriment is absorbed through the surface of the body The embryonic stages are usually not ciliated but are provided with six spines or hooklets Adult tapeworms are parasitic in vertebrates, but larval stages occur in both vertebrates and invertebrates

Whether the tapeworm represents an individual or a colony of individual all derived from the parent head portion or scolex is a question of academic interest rather than of practical importance However the entire tapeworm or strobila is regarded the fact remains that the scolex, being composed largely of actively growing germinative tissue, is continually giving rise to new seg

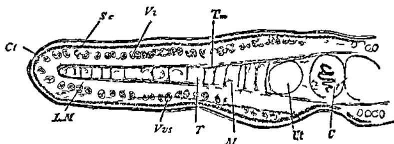


Fig 1 — Part of a transverse section through a proglottis of *Dibothriocephalus latus* *Ct* cuticle *C* cirrus *Vvs* vitelline follicles *LM* longitudinal muscle *T* testicles *M* medullary nerve *Sc* subcuticle *Tm* transverse muscles *Ut* uterus 20/1 (C [illegible])

ments or proglottides which commonly form a long chain The young undifferentiated proglottides will therefore be found near the scolex where segmentation is taking place further away the segments will show the sexual organs differentiated and the chain will be terminated with ripe segments filled with ova The proglottides may in some species form a chain of several thousands in others only a few remain attached to the scolex Ripe segments either singly or in groups may become separated eventually from the parent chain and be found in the stools

The terminal portion of the scolex is provided with muscular suckers (acetabula) or muscular grooves (bothria) and in some species with hooklets and other structures functioning in adhesion or fixation to the host This portion of the scolex is termed the head and the following non segmented portion the neck The head is said to be armed or unarmed, according to whether or not it is provided with hooklets

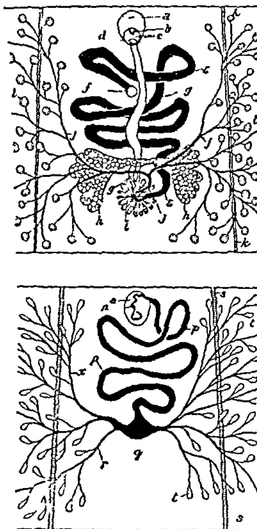


Fig 4 — *Diphyllobothrium latum* Upper figure female genitalia ventral view Lower figure male genitalia dorsal view The central portion only of the proglottis is shown *a* cirrus sac *b* partly everted cirrus *c* genital atrium and pore *d* vaginal pore *e* uterus *f* uterine pore *g* vagina *h* ovary *i* shell gland *j* vitelline duct *k* lateral nerve *l* vitellarium *n* vas deferens (muscular portion) *p* vas deferens *q* seminal vesicle and *x* vasa efferentia *s* lateral excretory canal *t* testicular follicles. (After Benham from Sommer and Landois) (*Courtesy of Wm Wood & Co*)

the cirrus pouch The latter opens into a larger cup-shaped cavity the genital atrium, into which the vagina also opens

The vagina extends from the genital atrium medially and posteriorly and usually in a general direction toward the ovarie It usually shows a dilatation which serves as a receptaculum seminis It opens into the common oviduct which connects with the ovary the latter being usually bilobed and situated posteriorly in the segment The oviduct after connecting with the vagina receives the vitelline ducts and passes on through the shell gland and continues as the uteru In certain tapeworms (Diphyllobothrium) the uterus consists of a simple tube which opens on the ventral surface of the body through the uterine pore In many species however the uterus shows very complex branching and is without an opening so that the ova are only liberated through the disintegration of the segment The yolk glands are follicular in character and situated near the posterior border of the segment

The adult worms occur in the alimentary tract of vertebrates and in mammals are almost wholly restricted to the small intestine The eggs of species possessing a uterine pore are discharged into the intestinal contents but those of

They discharge separately from the posterior border of the last segment, except when this represents the first segment formed, when they unite to discharge from a single opening

The genital organs usually appear in the segment some time after its differentiation from the scolex The segments of all tapeworms with the exception of one genus are hermaphroditic The sexual organs develop gradually and are

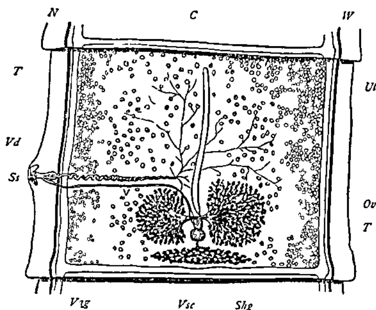


Fig 3 —Proglottis of *Tænia saginata* Goeze showing genitalia *C* transverse excretory canal *N* lateral longitudinal nerve *W* longitudinal excretory canal *T* testicles scattered throughout the proglottis *Ut* opposite the central uterine stem (a closed sac) *Ss* genital pore leading into the genital sinus above the cirrus and coiled vas deferens (*Vd*) below the vagina (*Vag*) bearing near its termination a dilatation the seminal receptacle *Vsc* the triangular vitellarium and above it (*Shg*) the shell gland leading from this to the uterus is seen the short uterine canal on either side of this the two lobes of the ovary (*Ov*) 10/1
(C l y / ll m B ol & C)

found in the mature state at some distance from the scolex The male organs usually develop earlier than the female and in many species both are eventually replaced in the ripe segment by the uterus as it becomes distended with eggs The testes are present in large numbers and are usually dorsally situated in the medullary layer They open into ducts vasa efferentia and these unite with one another to form the vas deferens which opens near the middle of the segment either at the lateral border or on its ventral surface This tube is usually much convoluted and is continuous with a protrusible organ, the cirrus which lies in

complexity of structure Thus the simplest type of cystic larvæ the *Cysticercus* is comprised of a sac or cyst in the wall of which there develops a single scolex or head There is in such forms no a exual multiplication in the larval state hence only one adult may arise from a given egg In another type of larva *Coenurus*, an indefinite number of scolices may arise from the wall of the cyst and it may accordingly give rise to as many adults Finally asexual multiplication may go still further in the *Echinococcus* type of larva in which daughter cysts may develop and in these great numbers of brood capsules each of which may enc ose several or a large number of scolices In order for such larval forms to develop further their ingestion by the species serving as primary host is necessary and is ordinarily accomplished through the eating of uncooked flesh

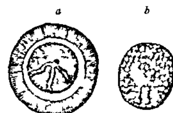


FIG 6 —*a* onc phere in its radially triated embryophore (erroneously termed egg shell) of *Tænia africana* Greatly magnified (After von Lin tow) *b* (freed oncosphere of *Dipylidi n ca n um* (After Grassi and Rovelli) Both oncospheres show ix spines (*C u y f* *H m H d C*)

Certain tapeworms are apparently not markedly injuriou to their host Others give rise to toxic products which may produce a profound anemia The larval forms developing in various organs may also produce serious conditions

DIPHYLLOBOTHRIIDÆ

This family is represented by species of two different genera that are parasitic in the adult state in man The human body may also be invaded by the plerocercoid larvæ of some species

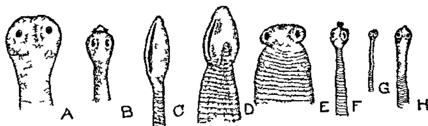


FIG 7 — Heads of some adult tapeworms found in man drawn to scale *A* beef tapeworm *Tænia sagin t* *B* pork tapeworm *T s l um* *C* fish tapeworm *Diphyll both iu latum* *D* heart head d tapeworm *D phyll b th i i c datum* *E* African tap wo m *T f cana* *F* double pored dog tapeworm *Dipyl d n a nun* *G* dwarf tapeworm *Hymenolep s nana* *H* rat tapeworm *Hymen lep s diminuta* × 10 (*C I y J h B I y & S*)

other species are liberated when the segments disintegrate in the feces For most tapeworms a secondary host is necessary, either another vertebrate or in some instances an invertebrate Fecundation may be accomplished either through the copulation between the segments of different worms or between different segments of the same worm, and autofecundation may also take place

Two different types of eggs are produced The Diphyllobothriidæ produce ovoid operculated eggs containing fertilized ovum and yolk cells Eggs of other tapeworms have a more complicated structure and development They consist at first of fertilized ovum and yolk cells enclosed within a delicate shell Later on an embryo develops and a rather thick secondary membrane is formed upon the surface of the latter The structures external to the embryo and its membrane are in the eggs of Tæniidæ deciduous but are retained in Hymenolepididæ The embryo with its surrounding membrane is termed the oncosphere

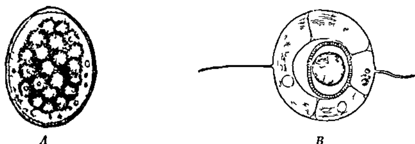


FIG 5 — A Egg of *Diplogonoporus grandis* showing the morula surrounded by yolk cells and granules 440 1 (After Kurimoto)
B Uterine egg of *Tænia saginata* G Uterine shell with filaments the oncosphere with embryonal shell (embryophore) in the center 500/1 (After Leuckart) (*Courtesy of Wm Wood & C*)

and three pairs of hooklets are usually visible within Further development of the embryo only takes place when ingested in some manner, as in contaminated food or water by its proper intermediate host After entering the alimentary tract of the latter the embryos escape from the membrane and penetrate the tissues where they develop into the larval stages

The larval forms which arise from the growth of the oncospheres are of two types (1) those which are solid and which are eventually transformed directly into adult tapeworms (2) those which are transformed into cysts from which the scolices that are destined to grow into adults, develop secondarily With the first type of development in which there is no cyst formation, we may have a rounded or ovoid larva *Plerocercus* or a wormlike larva, *Plerocercoid*, such as is seen in *Diphyllobothrium latum* the 'broad' tapeworm In the second type of development the larva may show only a rudimentary cyst cavity and is then known as a *Cysticercoid* or the oncospheres may be transformed into characteristically cystic larvæ which are further classified on the basis of their

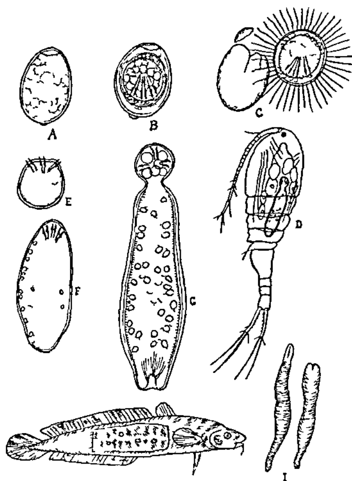


FIG 8 — Development of *D ph llobothrium latum* outside of the human body 1 The unripe egg showing the con picuous p r lum and at the oppos te end a rudimentary knob hich as ist in the d ag no s *B* An egg ready to hatch showing the enclosed hexacanth c liated embryo C The escape of the embryo (*coracidia*) *D* When *ingested by Cy lops strenuus it develops further as shown here in its* final sta e of development *E* An early stage of the larva after it h s lost its ciliated envelope and penetrated into the body ca ty of Cyclops *F* A gro in form *G* The procerco d larva wh ch atta ns its maximum *size after twenty days in body cavity of Cyclops H* A burbot which has become para tized by ingesting the infested *Cyclop* the plerocercoids being p esent in the mus les a well as in the internal organs *I* Plerocerco ds removed from the fi h show ng o e with head e tend d the other with head in a inated Mod fed after Brumpt

Diphyllobothrium latum

Diphyllobothrium latum, the 'broad tapeworm" or "fish tapeworm' so called, is widely distributed in Europe especially around the Baltic, in Poland Roumania and Switzerland, and occasionally in other regions It is said to be especially frequent in Japan and Turkestan, is reported from parts of Africa and it has also established itself in North America to the west of the Great Lakes This worm is unusually long lived and cases are on record in which it had been present in the human being over a period of sixteen years, since there had been during this time no opportunity for acquiring the parasite On account of its long life it is frequently found in emigrants long after they have left the regions in which the parasite was acquired

There are frequently no serious symptoms associated with the presence of this worm at least for long periods Occasionally however, it causes a very severe anemia which closely resembles pernicious anemia, except that improvement and recovery usually follow the expulsion of the worm

Diphyllobothrium latum Linnaeus, 1748 measures from two to nine meters and is of whitish gray color with yellowish tinge The head is almond shaped flattened laterally with deep grooves or bothria in its dorsal and ventral borders and the neck is very slender The proglottides may number three or four thousand and with exception of the older segments are broader than they are long Somewhat centrally situated in each segment is a dark spot that marks the situation of the rosette like loops of the uterus The numerous testes which are situated dorsally in the medullary portion of the segment empty into vasa efferentia which unite to form the vas deferens The latter terminates in a cirrus which is enclosed within a large cup shaped cirrus pouch opening on the ventral surface near the anterior border of the segment The vagina which opens close behind the male orifice extends backward in the median line and widens to form a receptaculum seminis before joining the oviduct The ovary is bilobed and wing shaped with the shell gland lying posteriorly between the two lobes The follicles of the vitellaria are distributed throughout in the cortical layer

The eggs are large ovoid with thick brownish shells having inconspicuous lids The embryo is only slightly developed and surrounded by yolk cells A fortnight or more after the eggs are deposited in water the shells are burst by the ciliated hexacanth organism which has developed within That the ciliated larva undergoes further development in certain fresh water copepod *Cyclops strenuus* and *Diaptomus gracilis* has been demonstrated by the works of Rosen and Janicki (1917–1918) On being ingested by these crustacea the larvæ pass into the body cavity increase in size and are transformed into procercoid shedding the six hooklets from their posterior end and developing a cephalic invagination The ingestion of the parasitized copepods by various fresh water

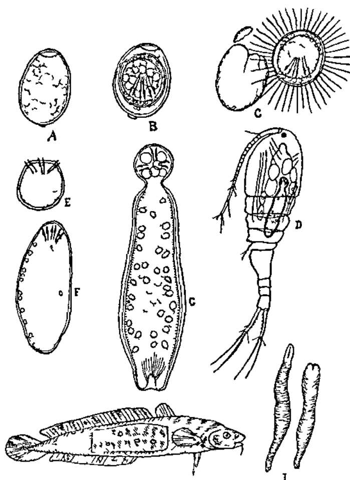


FIG 8 —Development of *Diphyllobothrium latum* outside of the human body A The unripe egg showing the conspicuous operculum and at the opposite end a rudimentary knob which assists in the diagnosis B An egg ready to hatch showing the enclosed hexacanth ciliated embryo C The escape of the embryo (*coracidium*) D When ingested by *Cyclops strenuus* it develops further as shown here in its final stage of development E An early stage of the larva after it has lost its ciliated envelope and penetrated into the body cavity of Cyclops F A growing form G The procercoid larva which attains its maximum size after twenty days in body cavity of *Cyclops* H A burbot which has become parasitized by ingesting the infested *Cyclops* the plerocercoids being present in the muscles as well as in the internal organs I Plerocercoids removed from the fish showing one with head extended and the other with head invaginated Modified after Brumpt

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the peritoneal cavity and finally to the muscles In certain localities from 0 to 40 per cent of the frogs were found to be parasitized and on feeding such frogs to dogs adult worms were obtained in 15 days The plerocercoides are also found in snakes ducks chickens rats boars cats pigs and monkeys as well as the human being The adults have been recovered from cats dogs and man



FIG 11 — *Sparganum Proliferum* × 10 (After Stiles) (C I J H m B d C)

Sparganum proliferum Ijima[4] produces an acne like condition of the skin and may occur in great numbers throughout the various organs and tissues of the body It is characterized by its irregular shape numerous heads being produced which become detached and wander through the tissues It has been reported from Japan and Florida Its adult form has not been discovered

The genus *Diplogonoporus* is characterized by a short scolex with powerful suctorial grooves and no neck The segments are short and broad and each contains two sets of genital organs which are essentially similar to the single one of *Dibothriocephalus* *Diplogonoporus grandis* occurs in the adult state in whales and seals and has been found in the human being in Japan

DIPYLIDIIDÆ

Dipylidium caninum Linnæus 1738 is a common parasite of the dog and is only occasionally found in the human being most frequently in young children The segments leave the rectum of the dog spontaneously and creep about so

fishes is followed by further development of the larvæ which now grows to one or two centimeters in length and assumes a worm like form known as the plerocercoid. The latter is found more frequently in the viscera than in the musculature of the fish (Brumpt[1]). It is through the ingestion of the plerocercoid in either raw or improperly cooked fish, that it is transmitted to its definitive host. The adult worm occurs in the dog, the fox and the cat as well as in man, and it is common for a single individual to harbor several or even a large number.



Fig. 9.—Cephalic end of *Sparganum mansoni* Cobb. (After Leuckart.) (Courtesy W. Wood & Co.)

Dibothriocephalus parvus Stephens 1908 is described as a small worm, its largest segments measuring only 5 x 3 mm. Eggs average 59.2 x 40.7 μ. It has been reported as occurring in a Syrian in Tasmania.

Dibothriocephalus cordatus R. Leuckart, 1863 occurs commonly in seals and dogs in Greenland, rarely in man.

Sparganum mansoni.—Bothriocephalid larvæ have been found in several cases in man. Since the adult forms were unknown the generic name *Sparganum* Diesing 1854, was applied to such forms. *S. mansoni* Cobbold, 1883, was discovered by Patrick Manson in the course of an autopsy on a Chinaman. The plerocercoids are somewhat ribbon shaped, may attain a length of 30 cm. and are from 3 to 12 mm. in width. They have been found beneath the peritoneum, in the abdominal cavity, in swellings of the skin and they may be passed in the urine. They occur most frequently in the eye and in the genito urinary tract. This parasite has a wide geographical distribution being found in the southern United States and Australia but is most frequently encountered in parts of China and Japan.

The complete life cycle has been worked out by Japanese investigators. Yamanada and S. Yoshida[2] (1917) by feeding *Sparganum mansoni* to dogs obtained adult *Diphyllobothria*. The early larval development was demonstrated by T. Okumura[3] (1919) in *Cyclops leukarti*. When parasitized individuals of this crustacean were fed to frogs or mice, the larvæ penetrated the intestinal wall and passed to



Fig. 10.—*Sparganum mansoni*; on the right in transverse section. Natural size. (After Ijima and Murata.) (Courtesy W. Wood & Co.)

the peritoneal cavity and finally to the muscles In certain localities from 30 to 40 per cent of the frogs were found to be parasitized and on feeding such frogs to dogs adult worms were obtained in 15 days The plerocercoides are also found in snakes ducks chickens rats boars cats pigs and monkeys as well as the human being The adults have been recovered from cats dogs and man



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that they eventually get into the fur where they may dry and disintegrate Th oncospheres may then be taken up by the dog louse *Trichodectes canis*, or by fleas, *Ctenocephalus canis* and *Pulex irritans*, in which they develop into cysticercoid larvæ Dogs become infected through the agency of their own ectoparasites by biting at the latter in their fur, and it is evidently transmitted to the human being through the ingestion of food into which a flea has fallen

HYMENOLEPIDIDÆ

Hymenolepis nana or "dwarf tapeworm," first found to be common in Sicily and parts of Italy is apparently also very widely distributed throughout the world being reported from North and South America as well as from various parts of Europe and Asia Notwithstanding its small size, when present in large numbers it causes rather pronounced symptoms, as loss of appetite diarrhea, nervous symptoms, etc , all of which disappear with the expulsion of the parasites

Hymenolepis (fraterna) murina Dujardin which is believed by some authorities to be identical with *H nana* or at most only a variety of the latter, occurs in rats and mice Although anatomically identical, it is not possible to infect rats with the dwarf tapeworm of the human being or vice versa According to Grassi development may be completed without an intermediate host Larval forms of the worm occur imbedded in the intestinal mucosa of the rat These grow into adults in about fifteen days from the time that the oncospheres are ingested While it is not possible to follow the stages of development of *H nana* in human beings it has been determined experimentally that infection is direct in them as well as in rodents The great numbers of worms found may therefore be accounted for by direct reinfection (autoinfection)

Hymenolepis diminuta a considerably larger (20 to 60 cm in length) tapeworm than the preceding species occurs ordinarily in the rat but has been found in a small number of cases in human beings The larval form (cysticercus) is found in a great variety of insects but most commonly in a small moth, *Asopia farinalis* also in fleas and meal bugs

DAVAINEIDÆ

Only a small number of cases of the occurrence of this species in man have been reported

TÆNIIDÆ

Tænia solium

The adult form of this species occurs only in the human being Its larval stage *Cysticercus cellulosæ* occurs normally in the striated muscles of the

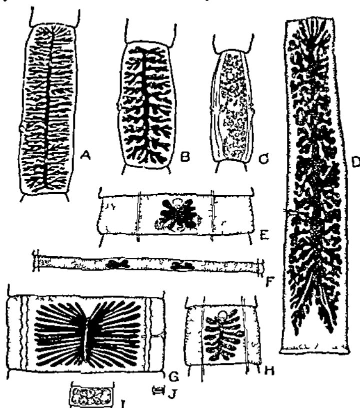


FIG 12 — Ripe proglottids of various tapeworms of man drawn to scale according to average measurements A *Tenia s ginata* (after Leuckart) B *Tæ ia s l i* (aft r Stiles) C *D pylidi i ca i u m* (after Diamare) D *Tænia co ifusa* (after Guyer) E *Dipl yllob th ri m latum* (after Leuckart) F *Dipl go oporus grandis* (after Ijma and Kurimoto) G *Diphyll both i m c rdatum* (after Leuckart) H *Tænia af ica a* (after on L nstow) I *Hyme lepis dimi ta* (after Crassi) J *Hym lepis nana* (after Leuckart)

(C i y f J h B l y & S)

domestic pig but is known to exist also in the wild boar as well as in the stag dog cat brown bear monkey and not infrequently in man The cysticercus which develops in the pig is an ellipsoidal vesicle measuring from 6 to 20 mm

by from 5 to 10 mm The head develops in the wall of this vesicle and may be either invaginated or protruded with reference to the remainder of the vesicle The human being acquires the parasite through eating measly pork' which has not been cooked sufficiently to kill the larvæ The danger of this species to the human being is not so much due to the presence of the adult worm as to the invasion of the tissues by its larval forms The latter may be acquired by the ingestion of oncospheres contaminating the hands, articles of food or drinking water It is thought that autoinfection may take place also not only by the contamination of the hands with oncospheres but also through the regurgitation of mature segments into the stomach in the course of vomiting In such instances the development of the oncospheres might proceed in the same manner as though they had been introduced through the mouth An individual harboring the pork tapeworm, therefore should be regarded as a menace both to himself and to others Measures should accordingly be taken to destroy all parasites evacuated with the stools, and personal cleanliness should be insisted upon The transmission of the worm from the human being to pigs is undoubtedly facilitated by allowing the latter free access to privies a custom which prevails in various parts of the world This species is rare in the United States and in most of the cases in which it has been reported *Tænia saginata* has probably been mistaken for it Stiles found only one specimen of *T solium* in several hundred human tapeworms although it has since been reported in the Southwest It is more common in countries where pork products are eaten raw or insufficiently cooked This parasite has become less frequent than formerly in North and East Germany on account of the precautions taken to avoid trichiniasis Regulations have been enforced so that measly meat although it may be sold as such must be thoroughly cooked before being placed upon the market or if badly infested it is required that it be used for industrial purposes rather than for food

Tænia solium Linnæus 1767 the so-called ' pork tapeworm, measures about 2 to 3 meters in length and occasionally more the head is globular with the rostellum armed with a double circlet of hooks usually about twenty six to twenty-eight in number The neck is rather thin and long and proglottides which number from 800 to 900 increase in size very gradually The genital pores are situated at the lateral margin a little behind the middle of the segment and alternate fairly evenly The mature segment measures from 10 to 12 mm in length by 5 to 6 mm in breadth, and shows a uterus consisting of a median trunk with from seven to ten lateral branches on either side some of which are again ramified The eggs are spheroidal and have an outer shell which is thin and delicate and a thick embryonal shell with radial striations The eggs measure from 31 to 36 microns in diameter and the oncospheres which are each provided with six hooks measure about o microns in diameter

The larval form of *T solium* *Cysticercus cellulosæ* has been found in practically all organs of the human body It occurs most frequently in the brain and next frequently in the eye in the muscular system the heart subcutaneous tissue liver lungs and abdominal cavity Some cases show only a single example of the parasite others may show thousands Males are most frequently attacked from sixty to sixty five per cent of the cases being of this sex The disturbances caused by these parasites vary according to their location in the body especially with reference to the organ in which they are located When situated in the meninges their effect is similar to that of tumors In the eye they not only interfere with vision but are extremely difficult to remove so that the function of the eye is usually destroyed (De Schweinitz and Wiener)

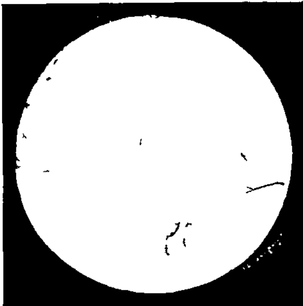


FIG 13 — Cysticercus cellulosæ of the vitreous (After de Schweinitz and Wiener)

Tænia saginata

Tænia saginata or the beef tapeworm lives in the adult state only in the human intestine and in its larval form *cysticercus bovis* almost exclusively in the ox The cyst occurs more frequently in the pterygoid muscles than elsewhere so that it may be readily overlooked It is the most common tapeworm of man and is widely distributed throughout the world being absent from regions where beef is not utilized as food The cysticerci of this species are killed by brief exposure to low temperatures so that cold storage has proved an effective measure in the eradication of this worm Ransom has found that exposure to 14 to 15° C for four or five hours is sufficient to destroy *Cysticercus bovis* This parasite is probably usually destroyed in cooking only escaping in uncooked portions of meat or in instances in which raw beef enters in the diet

Tænia saginata Goeze 1782 may attain a length of 10 meters or more

even 36 meters has been reported The head is somewhat cuboidal in shape and is unarmed The four suckers are hemispherical and in place of a rostellum there is a sucker like organ The neck is moderately long and about half as wide as the head The genital pores a ternate irregularly and are situated somewhat behind the middle of the lateral border of the segment The mature detached proglottid resembles a pumpkin seed and measures from 16 to 6 mm in length by 4 to 7 mm in breadth The uterus shows from twenty to thirty five branches on each side of the median trunk and these may ramify further The eggs are globular the outer layer often remaining intact and showing one or two filaments The embryonal shell is ovoid in shape thick and radially striated and measures from 30 to 40 μ in length and from 20 to 30 μ in width The cysticercus, or larval stage measures from 7 5 to 9 mm in length by 5 5 mm. in breadth and consists of a vesicle with a single scolex

Treatment of Tapeworms

The treatment for the various types of cestodes found in the intestinal tract is the same The most essential thing is the preparation of the patient He should be kept at rest under observation for three days The day the vermifuge is given should be spent in bed For the first day the patient is placed on a liquid diet The first night 30 c c of castor oil is given The following day at 4 P M 30 grams of magnesium sulphate in 200 c c of water is given The third morning the vermifuge is administered on an empty stomach at 8 A M The drug of choice is *Aspidium Felix Mas* the ethereal extract of male fern The drug must be freshly prepared Give 2 c c of the drug in hard gelatine capsule for three successive doses at 8 A M 8 30 A M and 9 A M The total dose is 6 c c At 11 A M a good purge of magnesium sulphate (15 grams) in a full glass of water is administered to wash out the worm In case the worm does not appear soon after the final aperient 2 c c of carbon tetrachloride may be administered followed in one hour by a saline purge of 15 to 20 grams of sodium sulphate The treatment can be modified somewhat for the smaller tænias *Tænia diminuta* is readily removed with small doses of *Aspidium Felix Mas*, sometimes being eliminated by vigorous purgation *Hymenolepis nana* does not require rigid preparation One day on a liquid diet with a saline purge at night followed by *Aspidium Felix Mas* the following morning is quite sufficient to remove these parasites

Prophylaxis for Tapeworms

The essential factors in prevention of *Tænia solium* or *Tænia saginata* are first the proper disposal of human feces and secondly an adequate method of

meat inspection Personal prophylaxis is the avoidance of uncooked or partially cooked meat The cysticerci are readily killed by refrigeration so that infected meat is rendered safe if held in refrigeration at a temperature not exceeding 15 F for 15 days (beef) and 21 days (pork) The proper cooking of all fresh water fish utilized as food is sufficient to prevent the development of *Diphyllobothrium latum*

Echinococcus

Tænia echinococcus in its adult form lives in the small intestine of the dog the wolf the jackal and other related species The larval stage *Echinococcus (polymorphus) unilocularis* occurs in the organs chiefly in the liver and lungs of numerous species of mammals as for example sheep the ox the pig and not uncommonly in man In Australia the parasite is maintained through the prevalence of rabbits which serve as food for the dog and also as intermediate host for this parasite The eggs of this worm are disseminated with the feces of dogs which harbor the adult form They are transmitted to the human being by the contaminative method as by allowing dogs to lick them or by eating from dishes which have been licked out by dogs The occurrence of echinococcus cysts in man should always be regarded as serious These cysts grow gradually to considerable size frequently to the size of a child s head and in some instances produce sloughing and may discharge into the bronchi or elsewhere

Tænia echinococcus von Siebold 1853 The dog tapeworm is very minute measuring only 2 5 to 5 or 6 mm in length The head is 0 3 mm in breadth and shows a double row of hooklets on the rostellum The neck is short and there are only three or four segments of which only the posterior one is mature This measures about 2 mm in length and 0 5 mm in breadth The genital pores alternate the ovary is horseshoe shaped with concavity directed backward The uterus shows a median trunk filled with eggs as well as lateral diverticula The embryonal shell of the egg is moderately thin with radial striae It is of globular shape and measures from 30 to 36 μ in diameter

The echinococcus cyst or hydatid *Echinococcus unilocularis* originates through the liquefaction of the interior of the onco phere or embryo It then grows slowly to considerable size in the hog to 4 or 5 cm in cattle to the size of an orange and in man a somewhat larger size may be attained The wall of the cystic larval form is composed of an external laminated cuticle and an internal germinative or parenchymatous layer These two layers may be followed throughout all subsequent development in which various structures are produced

by a process of invagination The final products of development are brood capsules containing a number of scolices, each of which is capable of developing into an adult worm, if ingested by its proper host, the dog The course of development, however differs widely The echinococcus cyst in its simplest form shows numerous brood capsules, which develop by infolding of the wall of the cyst. The scolices are produced by further invagination in the wall of the brood capsule A large mother cyst may contain many thousands of the minute brood capsules each containing from two to thirty or more scolices With the rupture of the brood capsules the scolices may be disseminated throughout the cyst as hydatid sand In man, in place of the immediate production of brood capsules from the wall of the maternal cyst daughter cysts are produced which although somewhat smaller are in every other respect similar to the mature cyst These are said to originate from detached portions of parenchyma located between the laminæ of the cuticle according to some authors from a metamorphosis of scolices that have separated from the brood capsule by the transformation of brood capsules themselves and by the constriction off of portions of the wall of the mature cyst It has been determined that daughter cysts, transplanted into other animals continue to develop and give rise to brood capsules and scolices Even the scolices themselves when similarly transplanted, may undergo vesicular metamorphosis and then continue to propagate It is obvious from the results of experimentation that the dissemination of any portion of the hydatid during operative procedures may result in the further propagation of the parasite The development of the echinococcus cyst does not however always proceed normally Sterile cysts are produced in which no brood capsules or scolices develop The fluid contents of the cysts may become absorbed and its wall become infolded so as to appear as a mass of plicated hyaline laminæ

FIG 14 — *Tænia echinococcus* the cirrus sac the vagina uterus ovary shell gland and vitellarium and the testicles at the sides are recognizable in the second proglottis the posterior proglottis shows the uterus partly filled with eggs as well as the cirrus sac and the vagina. 50/1 (C [illegible])

This parasite is common in various regions of Europe Iceland Argentine Paraguay and Australia In the latter country the rabbit serves as the intermediate host and man is not infrequently attacked In Iceland the parasite is also very prevalent and it is said that 2 3 per cent of the inhabitants harbor echinococcus Its occurrence in man may be due to local customs with respect to the closenes of the association of man and dogs and also to a large extent to the prevalence of the parasite in dogs

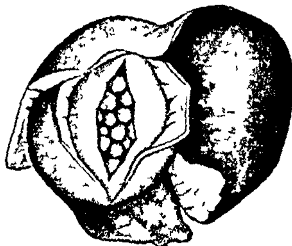


Fig 15 —Echinococcus (hydatid) cyst in the liver The fibrous capsule and the wall of the echinococcus have been incised so that the endogenous daughter cysts may be seen Reduced (After Ostertag from Thomas) (C ... y / Wm Wood & C)

Diagnosis —The diagnosis of the presence of echinococcus cyst is made by finding scolices or hooklets in material obtained by operation or in sputum or sloughing tissue The peculiar hyaline laminated membrane characteristic of the hydatid cyst is readily distinguished The presence of echinococcus cyst is also determined by complement deviation and by precipitin reaction the former being regarded as the more reliable has been employed in large hospitals as a routine diagnostic measure in case in which echinococcus is suspected The diagnosis of echinococcus disease has been greatly aided by the studies of the Australian scientists Drew Kellaway and Williams[67] Their diagnostic test is accomplished by the intracutaneous injection of 0 2 c c of sterile hydatid fluid which has been obtained by aseptic puncture of cysts from the lungs or liver of sheep A positive reaction present two phases an urticarial wheal and a delayed eryth

ema with edema of the subcutaneous tissues The test is more reliable than complement fixation and in pre operative or doubtful cases it is of great value In post operative or even cured cases the test remains positive for a long period The authors cite an instance in which the test was positive 16 years after cure

Treatment — The accepted treatment for echinococcus disease is surgical However it should be borne in mind in the course of all operative procedures that the rupture of a cyst into a serous cavity may be followed by serious symptoms and collapse Furthermore, cysts that are incompletely removed may continue to develop and operative procedures may also serve to disseminate the disease The X ray has been employed with the view of causing the absorption of hydatids but the value of this form of treatment has not yet been definitely established

Tænia multilocularis is now generally accepted as a distinct species from the preceding Not only the adult worm as it occurs in the dog, differs in length size and number of hooklets and conformation of the uterus, but more important is the peculiar character of the larval form and its restricted geographical distribution Except as it occurs in emigrants this parasite is known to occur only in southern Bavaria, Tyrol, Wurttemberg northern Switzerland and in certain districts of Russia and Siberia The larval form *Echinococcus alveolaris* or *multilocularis* is said to occur in those caring for sheep rather than in those having the care of cattle The larva grows irregularly extending processes which infiltrate the host tissue in all directions In fact it was originally regarded as a tumor until its parasitic nature was established by R Virchow The formation of cuticle is of secondary importance but cystic cavities are eventually formed varying from 1 5 mm to several cm in diameter, so that the cut surface presents a honeycombed appearance The progno is in cases of *T multilocularis* is bad a single case of cure being recorded by Bruns which in this instance was accomplished by radical resection of liver

Fig 16 — A piece of the wall of an *Echinococcus unilocularis* stretched out and seen from the internal surface A few brood capsules (the outline of which is only faintly shown) with scolices directed towards their interior and exterior 50/1 (*Courtesy of W m Wood & Co*)

Meggitt s[8] treatise on tapeworms may be useful to those engaged in special studies or in identifying doubtful species of this class of parasites

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Sept 1 1927

CHAPTER XL

THE RELATION OF INSECTS AND OTHER ARTHROPODS TO DISEASE

By E. E. Tyzzer

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Introduction

In the following brief survey no attempt will be made to classify or describe the numerous species of arthropods concerned in the transmission or production of disease in the human being. The representatives of the phylum Arthropoda are characterized by the possession of jointed appendages or limbs. Respiration is effected through a system of tracheal tubes opening on the surface of the body. The deposition of chitin in the cuticle furnishes a more or less rigid exoskeleton. Included in this phylum are the classes Arachnoidea, which have head and thorax fused together, lack antennæ, and in the adult stage have four pairs of legs, and Insecta, which have head and thorax distinct, possess antennæ and have only three pairs of legs.

The mites, *Sarcoptidæ*, and ticks, *Ixodidæ*, are the more important families of the arachnoids from the medical point of view, while the insects are represented by the mosquitoes or *Culicidæ*, lice or *Pediculidæ*, bedbugs or *Acanthiidæ*,

winged bugs or *Reduviidæ* fleas or *Pulicidæ* and various families of biting and non biting flies In the following brief account of diseases either transmitted by or produced by arthropods scarcely more than mention is made of the species concerned A familiarity with the anatomy sufficient for the identification of the arthropods under consideration and a knowledge of their life history is however, of the utmost importance in the control of the disease with which they are associated The subject is adequately covered in a number of books of reference, any of which may be consulted for further information

VENOMOUS ARTHROPODS

The formidable appearance of various arthropods is sufficient to excite widespread though frequently groundless fear This is especially true when a wholly strange species is encountered Appearance is not however a safe index of whether a given form is dangerous or even harmful Thus with spiders those of the genus *Latrodectus* the venomous properties of which are well established are relatively small and insignificant while the so-called tarantulas (*Aviculariodea*) which have not been shown to be especially poisonous from their large size and active movements almost invariably inspire fear at least when first encountered Popular beliefs with respect to the poisonous properties of various arthropods are to a large extent based on fear rather than on actual observation or the latter may be so affected by fear as to be quite unreliable On the other hand it would be a mistake not to recognize the possibility of individual idiosyncrasies and conditions of hypersusceptibility to venoms so mild as to be ordinarily regarded of little consequence Thus some individuals show no reaction to the bites of a given species of flea which on others produce visible wheals which itch intolerably and persist for many days

A bee sting is usually a matter of slight consequence to the professional apiarist but there are reputed instances of death caused by a single sting In a case observed by the author a boy stung on the ear by a honey bee developed in the course of an hour great swelling of the nose the chin and the supra orbital ridges and a profuse urticarial eruption over the entire body Headache was complained of but unfortunately no exact clinical observations were made The eruption began to fade in the course of four or five hours and the general condition rapidly improved although a phlyctenular conjunctivitis followed About a week later this boy on being stung again by a honey bee showed only the usual local swelling evidently being no longer hypersensitive to the venom

The injuries inflicted by arthropods are produced in various ways The bites of certain species are of themselves painful and the mechanical injury is com

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affected than adults and the mortality of under five years of age is high The treatment employed is to apply a ligature above the sting so as to retard the dissemination of the venom The wound is then opened or excised Some progress has been made in the preparation of an antivenin that obtained appearing to have a beneficial effect

Nettling hairs are produced by the caterpillars of certain moths which cause a more or less serious rash on penetrating the epidermis The brown tail moth some years after its introduction into New England increased to such an extent that the dermatitis which it causes became very general The nettling hairs are needle pointed and possess recurrent barbs distributed in three longitudinal rows That their nettling property is not mechanical but due to an associated poison was indicated by their action on red blood corpuscles and demonstrated by treating them with various solvents (Tyzzer[1]) The nettling hairs of this species are blown about in dry weather and may thus lodge on clothing hung out to dry The flannel moth caterpillar (*Lagoa crispata*) found in the southern United States is also especially poisonous For further information on this and other urticating species a recent treatise by Foot[2] and books on Medical Entomology may be consulted

The body fluids of certain arthropods have pronounced irritating properties The most familiar example is that of cantharidin a volatile crystalline substance from the blood plasma of a blister beetle known as the Spanish fly The potency of cantharidin formerly extensively used on account of its vesicating properties is indicated by the fact that deaths are recorded as resulting from its external application It is said that while the blister beetle is not especially poisonous to poultry human beings may be poisoned by eating the flesh of poultry that have eaten it Poisons of this type are probably more widespread than is generally known although utilized by primitive people for arrow poison In the course of the study of the brown tail moth dermatitis it was found that the body fluid of the caterpillar produced a very pronounced reaction on the slightly scarified skin

The Transmission of Disease by Nonparasitic Species

These may serve as intermediate hosts for parasites of the human being as agents in the mechanical dissemination of pathogenic microorganisms and they may themselves in the larval stage appear in the role of accidental parasites The best examples of nonparasitic arthropods serving as intermediate hosts for human parasites occur in the CRUSTACEA The larval stages of the Guinea worm *Dracunculus medinensis* develop in certain species of *Cyclops* and the early development of the tapeworm *Diphyllobothrium latum* and *D mansoni* is found to occur in copepods of this genus Of the crustaceans various species

only enhanced by the injection of irritating or venomous material at the time of biting Certain bites are frequently followed by secondary infections of various degrees of intensity Although the spiders are popularly supposed to be quite generally venomous relatively few have been shown to be so and almost all of these are of the genus *Latrodectus* There is little doubt that bites of various species of this genus are associated with serious constitutional disturbances and it is quite possible that under exceptional conditions that they may cause deaths Certain of the true bugs or *Hemiptera*, are al o capable of inflicting painful wounds but in general are notably nonvenomous The bite of the familiar bedbug *Cimex lectularius* causes considerable reaction in certain individuals but is not noticeable with others Many of the biting flies doubtless secrete a saliva possessing poisonous properties thus the bites of both mosquitoes and black flies (*Simuliidæ*) result in lesions of varying degrees of severity While certain of the ants possess true stings with others the poison is introduced by biting Certain species found in tropical countries are said to cause constitutional symptoms as well as painful local reactions

Stinging is a form of injury inflicted by insects of the order *Hymenoptera* which includes the bees and ants In these the o ipo itor is modified to form the sting connected with which are specially differentiated poison glands. When the honey bee stings the tip of the abdomen is torn off, adhering to the sting after this is driven into the skin and the muscles attached continue to contract driving it deeper into the skin and compressing the poison glands. The instantaneou removal of the sting by scraping with the finger nail or with a knife if one is at hand is essential care being taken not to compress the part attached to the sting and force the poison into the skin Some bees such as the bumble bees are capable of withdrawing the sting from the skin and may thus use it repeatedly The stings of hornets and wasps are justly dreaded on account of their severity Many remedies are suggested which have in view the neutralization or destruction of the poison in bee stings but these are in general ineffective not being absorbed by the skin Cold applications may allay the pain and swelling to some extent and after the acute phase is past hot applications tend to hasten the reduction of swelling In cases of severe uticaria the injection of adrenalin may be considered but should be undertaken with caution With supportive treatment the more serious symptoms u ually ub ide in a short time

The scorpions which belong to the Arachnids (Arthropods with four pairs of legs) are also equipped with a sting which is carried on the last segment of the body This segment is provided with a pair of poison glands with ducts opening out near the tip of the terminal spine The venom of different species varies greatly in toxicity, and the amount injected by large scorpion is correspondingly greater than furnished by small individuals Children are more seriously

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These may serve as intermediate hosts for parasites of the human being as agents in the mechanical dissemination of pathogenic microorganisms and they may themselves in the larval stage appear in the role of accidental parasites The best examples of nonparasitic arthropods serving as intermediate hosts for human parasites occur in the CRUSTACEA The larval stages of the Guinea worm *Dracunculus mediensis* develop in certain species of *Cyclops* and the early development of the tapeworm *Diphyllobothrium latum* and *D mansoni* is found to occur in copepods of this genus Of the crustaceans various species

of crabs and crayfish serve as secondary intermediate hosts of certain of the flukes i e the larval stages of the lung fluke *Paragonimus ringeri* develop in *Potamon obusipes*, *P dehaani* and *Astacus japonicus* The molluscs serving as intermediate hosts for various species of flukes have already been discussed

In the dissemination of pathogenic bacteria, protozoa and higher parasites, the common house fly *Musca domestica*, on account of its habits of feeding upon human food as well as upon excrement and other discharges from the human body is without question an important agent It is undoubtedly a very important factor in the spread of typhoid fever cholera, bacillary dysentery, possibly leprosy and other bacterial diseases Stiles has demonstrated *Giardia* (*Lamblia*) cysts on flies which have fed on material containing this flagellate Wenyon and O Connor have obtained evidence that *Endamoeba histolytica* cysts may be disseminated by the house fly, although they have not succeeded in transmitting dysentery to kittens through this agent They found that such cysts were passed in some instances within fifteen minutes after being eaten by the fly but that under other conditions they were retained in the alimentary tract of the fly up to forty eight hours after ingestion The resistant forms of other intestinal protozoa as well as the ova of the larger intestinal parasites as *Tænia solium Ascaris lumbricoides* and *Oxyuris vermicularis* have been shown to be carried about by flies It is claimed that infectious ophthalmia (trachoma) is spread by the same agents

Other species of flies i e of the genus *Drosophila* may feed upon both fecal material and human food so that they may be considered as a possible agent in the dissemination of the parasitic organisms of the alimentary tract

Intestinal Myiasis

Intestinal myiasis is a condition resulting from the development in the alimentary tract of the larvæ of various species of dipterous insects The larvæ are derived from eggs deposited upon food The common blow flies (*Calliphora*) and blue bottle flies (*Lucilia*) deposit their eggs upon meat, especially when the latter is beginning to decompose, and flies of the genera *Musca* and *Anthomyia* may also deposit their eggs on food those of the latter genus usually on vegetable material The symptoms attending the development of larvæ in the intestine may simulate those of dysentery and be attended with more or less fever and malaise This condition is by no means rare in warm climates although it should be kept in mind that certain types of patients may undertake to deceive the physician Care should thus be taken to ascertain definitely whether the maggots are actually passed in the stools

Blow flies may also deposit their eggs in open wounds in the nostrils of those affected with ozena and occasionally in the external auditory meatus in

cases of otorrhea Cutaneous carcinomata not infrequently become infested with maggots even in temperate climates

The Screw Worm

The larva of a species of blue bottle fly *Lucilia macellaria* develops in the nasal cavity and occasionally in the external auditory canal Its presence is accompanied by great pain and discomfort and its migration to the frontal sinus may set up processes which result in meningitis and death As many as 350 larvae have been removed from a single case In some instances the soft palate and tissues about the nose have been destroyed Sneezing swelling of the face and a blood stained serous discharge from the nose are fairly constant symptoms Erysipelas may complicate the condition Instillations of ten per cent chloroform in milk or of oils kill the larvæ in the external auditory canal

Cutaneous Myiasis

Of the dipterous larva which may occur in the human skin certain species represent strayed parasites i e species which are normally parasitic for lower animals For other species both the human being and lower animals serve as satisfactory hosts The ox warble *Hypoderma bovis* or closely related species *H lineata* and *H diana* occur occasionally in man The eggs of this species are deposited by the adult fly on the hair of its normal host and on hatching are licked off by the animal and swallowed The larva migrate to the submucous tissue of the pharynx where they remain for several months and then migrate through various portions of the body including the spinal canal and finally come to rest beneath the skin which is penetrated in order to provide for free respiration apparently necessary at this stage of development After completing its development the larva escapes from the boil like lesion it has produced and entering the soil passes into the pupal stage It is claimed by some that the larvæ may enter the skin directly on hatching from the egg Another œstrid larva of the species *Dermatobia cyaniventris* occurs commonly in human beings in Brazil and other parts of South America where it is known as Ver Macaque It is now apparently well established that the eggs of this species are deposited by the adult fly on the bodies of certain mosquitoes of diurnal habits also upon various species of blood sucking flies and occasionally ticks so that the larvæ on emerging while the insect is feeding may then penetrate the skin of the victim A cluster of about fifteen or twenty eggs is cemented to each insect The migration of the larva may cause considerable pain and after it comes to rest beneath the skin produces a lesion which may attain the size of a pigeon s egg

of crabs and crayfish serve as secondary intermediate hosts of certain of the flukes, i e the larval stages of the lung fluke *Paragonimus ringeri*, develop in *Potamon obtusipes*, *P dehaani* and *Astacus japonicus* The molluscs serving as intermediate hosts for various species of flukes have already been discussed

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may also be transmitted by bringing the skin into contact with diseased organs so that cases of tularæmia thus appear from time to time in market men While the insect vector of the human infection is *C discalis* certain fleas and lice appear to be chiefly concerned in the transmission of the infection from rodent to rodent

Chrysops dimidiatus and *C silaceus* serve as intermediate host of the human parasite *Loa loa* and it is thought that the former may occasionally transmit sleeping sickness by direct mechanical transference of infected blood to normal individuals

A species of sandfly *P hlebotomus papatasii* transmits an acute disease known as three-day or phlebotomus fever The causal agent of this disease is unknown but about ten days is necessary for its development in the sandfly before the latter becomes infectious It has now been demonstrated that the organisms of both cutaneous and generalized types of leishmania is will develop in certain species of *Phlebotomus* but up to the present time the infection has not been produced experimentally by the bite of this insect neither is the epidemiology of the disease satisfactorily explained by sandfly transmission

The larvæ of one species of fly *Aucheromyia luteola* act as temporary parasites to the human being These are the Congo floor maggots which feed at night upon blood obtained by puncturing the human skin

Mosquitoes of various species transmit a number of very important pathogenic microorganisms and parasites for which they serve either as definitive or as intermediate hosts For the classification and description of mosquitoe see Fantham Stephens and Theobald Only those of the subfamily *Anophelinæ* serve as hosts for the parasites of malaria Anophelines known to be concerned in the transmission of malaria as well as others in which one or more of the three species of malaria parasite has been found to develop are included in the following table from Brumpt[3] (see next page)

Development of the malaria parasite takes place in the adult mosquito After sporogony has taken place in the gut wall of the insect the infectious forms of the parasite the sporozoites migrate to the salivary glands and the proboscis from whence they escape into the tissue during the act of biting The time necessary for this development to be completed varies with temperature and with the species of malaria parasite but under favorable conditions is not less than seven to ten days Up to this time a mosquito which has ingested malarial blood is incapable of transmitting the disease The malaria parasite has been found to develop in the species of Anopheles listed in the table but relatively few of these are of actual importance in the transmission of malaria in a given region thus in the United States *Anopheles quadrimaculatus* is the only species of any great consequence in the spread of this disease

Filaria bancrofti is also transmitted by the mosquito and the development

The human being also serves as a satisfactory host for the African skin maggot or Ver du Cayor This is the larva of the tumbu fly *Cordylobia anthropophaga* a species very prevalent in certain regions, notably in Natal The eggs are deposited upon clothing or upon the skin the fly being attracted by body odors and filth The larvæ hatch promptly in some instances within the body of the parent fly and penetrate the skin without causing any appreciable pain As the maggots grow beneath the skin considerable discomfort may result and boil like lesions are produced After attaining full size, about one half an inch they perforate the skin and on reaching the ground pass into the pupal stage of development Infants are especially liable to be attacked by the larvæ of this species of fly

Temporary Parasites, i e , Blood Sucking Insects, Mites and Ticks in the Transmission of Disease

Various species of biting flies produce painful or annoying conditions of the skin Comparatively few species, however are known to transmit disease Certain species of Tsetse flies serve as hosts for trypanosomes which are pathogenic to man and animals *Glossina palpalis* transmits *Trypanosoma gambiense* which causes the gambian form of sleeping sickness, and *Glossina morsitans* transmits *Trypanosoma rhodesiense* which causes the Rhodesian form of sleeping sickness and *Trypanosoma brucei*, which causes Nagana, a fatal disease of cattle On account of the active habits of the tsetse fly with respect to feeding trypanosomes may be transferred mechanically from host to host and it was this mode of transmission that was first demonstrated by Bruce for *Trypanosoma brucei* The trypanosomes however undergo definite phases of development within the fly in which they persist for a long time probably throughout the life of the insect which thus serves as a vector of the infection However it has been shown that the trypanosomes become established in only a small proportion (five per cent) of the tsetse flies which have fed upon the blood of cases of trypanosomiasis Another trypanosome disease e g , Surra, affecting domestic animals in parts of Asia is transmitted by biting flies of the genera *Stomoxys* and *Tabanus* although the development of the flagellate within these flies is less well known

The transmission of poliomyelitis by the stable fly, *Stomoxys calcitrans* was claimed but not satisfactorily demonstrated It has been proved however, that this fly may transmit anthrax as well as malignant pustule in animals and serves as the intermediate host of certain parasitic worms of domestic animals.

Tularæmia or Deer fly Fever is commonly transmitted by the bite of *Chrysops discalis* This infection which is not uncommon in the jack rabbit and in certain of the ground squirrels occurring in parts of the United States,

of the larval stages in the latter has already been discussed The mosquito in this instance serves as intermediate host since it harbors the larval forms of the parasite in question *Filaria bancrofti* is said to develop in the following species

ANOPHELINES

Anopheles maculipennis
Myzomyia funesta
Cellia argyrotarsis
Myzorhynchus minutus
Myzorhynchus nigerrimus
Myzomyia rossii
Pyretophorus costalis
Myzorhynchus sinensis
Myzorhynchus barbirostris
Myzorhynchus pedilaeniatus

CULICINES

Culex pipiens
Culex fatigans
Culex skusei
Culex gelidus
Culex sitiens
Culex albopictus
Stegomyia perplexa
Stegomyia fasciata
Stegomyia pseudoscutellaris (*Aedes variegatus*)
Stegomyia gracilis
Mansonioides uniformis
Mansonioides annulipes
Scutomyia albolineata
Taeniorhynchus domesticus

Yellow fever which according to investigations by Noguchi[4] would appear to be caused by a spiral organism *Leptospira icteroides* * is transmitted by *Aedes calopus* (*Stegomyia fasciata*), a culicine mosquito A period of development of about twelve days is necessary before the mosquito becomes infectious and for the mosquito to become infected it apparently is essential for it to draw blood during the first few days of the fever There is evidence that this and several other culicine mosquitoes transmit dengue fever

Recent studies by Sellard [5] and others fail to confirm this organism as the etiological agent

Anopheles Concerned in the Transmission of Malaria

Species of primary importance	Plasmodium*	Species of secondary importance	Plasmodium	Species which from their rarity biological peculiarities or feeble receptivity are of slight importance	Plasmodium
A (Nyssorhynchus) annulipes	*f*	*A crucians*	*vf*	*A (Myzorhynchus) barbirostris*	*vf*
A (Cellia) albimanus	*vf*	*A (Nyssorhynchus) fuliginosus*	*vm*	*A bifurcatus*	*vf*
A (Cellia) argyritarsis	*vf*	*A (Cycloleppteron) intermedius*	*f*	*A (Myzomyia?) formosaensis*	*f*
A (Myzomyia) costalis	*f*	*A (Cellia) Kochi*	*vf*	*A (Myzomyia) Hunteri*	*f*
A (Myzomyia) culicifacies	*vfm*	*A (Nyssorhynchus) Lindesayi*	*f*	*A (Myzomyia) indefinitus*	*vf*
A (Myzomyia) funestus	*fm*	*A minimus var aconitus*	*f*	*A (Nyssorhynchus) Karwari*	*f*
A (Myzomyia) f v Listoni	*vfm*	*A (Cellia) pharoensis*	*f*	*A (Nyssorhynchus) leucosphyrus*	*v*
A (Pseudomyzomyia) Ludlowi	*vfm*	*A pseudopunctipennis*	*f*	*A plumbeus*	*v*
A (Nyssorhynchus) maculipalpis	*f*	*A (Pyretophorus) superpictus*	*v*	*A (Cellia) pulcherrimus*	*f*
A maculipennis	*vfm*	*A (Cellia) tarsimaculatus*	*f*	*A (Pseudomyzomyia) Rossi*	*fm*
A (Myzomyia) minimus	*f*	*A (Nyssorhynchus) Theobaldi*	*fm*	*A (Myzorhynchus) sinensis*	*vfm*
A (Patagiamyia) punctipennis	*vf*	*A (Myzorhynchus) umbrosus*	*vf*	*A (Cellia) tessellatus*	*f*
A quadrimaculatus	*vfm*				
A (Nyssorhynchus) Stephensi	*fm*				
A (Myzomyia) Turkhudi	*vf*				

v = Plasmodium vivax f = P falciparum m = P malariae

of the larval stages in the latter has already been discussed. The mosquito in this instance serves as intermediate host since it harbors the larval forms of the parasite in question. *Filaria bancrofti* is said to develop in the following species:

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Myzorhynchus barbirostris
Myzorhynchus pseudopictus

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Culex pipiens
Culex fatigans
Culex skusei
Culex gelidus
Culex sitiens
Culex albopictus
Stegomyia perplexa
Stegomyia fasciata
Stegomyia pseudoscutellaris (*Aedes variegatus*)
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Recent studies by Sellards[5] and others fail to confirm this organism as the etiological agent.

The mosquito has been considered as a possible agent in the transmission of leishmaniasis but no more than a slight development of the flagellate has been obtained in this host

Of the bugs that habitually attack the human being the bedbug is most generally distributed The Indian species, *Cimex hemipterus (Rotundatus)* has been suspected by Patton [6] to serve as a host for *Leishmania donovani* the parasite of kala azar The transmission of this disease by the bedbug has not been demonstrated and considerable evidence has been collected con raindicating its possibility The organism of the Indian form of relapsing fever has been found to persist for four to seven days in this bug after it has been fed on the blood of infected monkeys The common bedbug *Cimex lectularius*, is incriminated in the transmission of the European form of relapsing fever although the louse appears to be the normal agent through which this is accomplished It is quite possible that the bedbug may serve in the mechanical transference of pathogenic microorganisms i e, those of leprosy syphilis etc It has been found that *B pestis* after development in them, may persist for many weeks

Reduviid bugs of the genus *Triatoma (Conorhinus)* not only inflict painful wounds but *T megista* and a number of related species transmit a form of trypanosomiasis found in Brazil Many species of this genus have been found to harbor trypanosomes (Kofoid and McCulloch [7]) and some of the latter appear to be capable of infecting rodents and other wild animals so that it is not yet known how many of these bugs are capable of transmitting their tryanosomes to the human being Further investigations are also necessary in order to definitely differentiate the species of trypanosomes which have been found

Various species of Harvest mites *Trombidiidae* while only temporarily parasitic upon the human skin produce extremely annoying irritations and eruptions Quite a number of cases of Pediculoides ventricosus itch are now reported in the literature of various countries This is normally a parasite of insects but when the latter are not available the mite may attack the human being producing papillar or vesicular rash or even constitutional symptoms The skin is usually attacked by the larval (six legged) stages of such mites and owing to the small size of these pests the skin may be overrun before their presence is realized The larval stage of a Japanese mite *Trombidium akamushi* is known to transmit a very fatal typhus like disease known as Kedani or flood fever (Kitashima and Miyajima [8]) This species feeds in great numbers on the local field mouse *Microtus montebelloi* Inclusions known as Akamushi bodies have been reported in the tissues of both infected animals and of the larval mites There appears to be some doubt as to whether or not these bodies represent the etiological agent in the disease The virus is not filterable

The ticks *Ixodidae* are responsible for a disease known as Tick Paralysis' This occurs most frequently in sheep but also in children Bites over the verte

bral column especially near the head are more prone to be followed by paralysis This disease is associated with the bites of various species of ticks and occurs in Oregon British Columbia Australia and South Africa There is usually an incubation period of six or seven days before the paralysis appears The legs are first affected, later the arms thorax and neck There is little or no fever and in non fatal cases rapid recovery occurs The removal of the ticks appears to have a favorable influence on the course of the disease It is not definitely known whether this represents an infectious disease or the effects of toxic substances derived from the ticks Serious ulcerations may arise from the bites of certain species of ticks Rocky Mountain fever a typhus like disease having a high mortality is transmitted by *Dermacentor venustus* A *Rickettsia* is found in great numbers in the lesions in the wall of blood vessels and also in infected ticks which is considered by Wolbach[9] to represent the causal agent The organism of this disease has not been cultivated

African tick fever or relapsing fever is transmitted by *Ornithodorus moubata* It has been found that *Spirochaeta duttoni* persists through successive generations of this tick so that the latter may be regarded as its normal host

Ticks are responsible for the transmission of many diseases of domestic animals due to piroplasmata and it was in Texas fever that the transmission of an infectious disease through the agency of an invertebrate host was first demonstrated by Theobald Smith

Adapted Parasites — Ectoparasites and Disease

Itch Mite — The Itch mite *Sarcoptes scabiei* develops only on the skin of its host The itch mites of various animals are regarded as varieties of a single species Certain of these when transferred from animals to the human being may cause more or less itching and irritation but being unable to breed except on their normal host soon disappear The male of the itch mite measures only about 0 25 mm and the female 0 4 mm The former dies off after copulation but the impregnated females burrow into the epidermis and produce characteristic lesions distributed chiefly between the fingers and toes in the groins axillae and on the external genitalia but becoming more generalized in severe cases The burrows are slightly colored by the eggs and excrement deposited by the female and measure from a few millimeters to several centimeters From fifteen to fifty eggs are deposited by each female and a new generation is produced in about four weeks time This parasite is disseminated chiefly by contact or in fact by any means which effects the transference of the larvæ in any stage of, adults or of eggs although the latter probably occurs only rarely Scabies assumed great importance during the recent World War becoming widespread as great numbers of human beings were brought

together under imperfect sanitary conditions Sulphur ointment is commonly employed in the treatment of scabies It is possible to cure this condition by a single treatment through the employment of the 24 hour Danish method For details of the preparation of the ointment and the method of its application it is best to consult special articles on the subject (Lombolt[10], 19 0 and Greenwood[11] 1924)

Tongue Worms — *Linguatulidae* or tongue worms," so named from their characteristic shape are related to the mites but owing to their adaptation to parasitic life have lost nearly all resemblance to this group The body shows a large number of segments and at the head there are two pairs of claw like hooks situated at the sides of the oral aperture The adults live in the nasal cavity chiefly of the dog and other carnivorous animals and the eggs when deposited are discharged in sneezing They develop when ingested by herbivorous animals in which the larval stages are found in the liver and other organs As the larvæ approach maturity they migrate through the tissues to mucous surfaces and may leave their intermediate host in discharges from the respiratory tract or alimentary canal This however does not appear necessary for their transference since they may be ingested in great numbers with the flesh devoured by carnivorous animals The species most commonly found in man is *Linguatula rhinaria* but its occurrence is relatively rare and it is nowhere very prevalent in animals

Lice — These parasites assume great importance under conditions of war Their presence is not only a source of annoyance to those not accustomed to them but as disease transmitters they are concerned in epidemics which incapacitate and decimate great populations Lice are wingless insects adapted to life on the surface of the body and feed upon the blood of their host There are two types of these insects infesting the human being, the true louse *Pediculus* and the pubic or crab louse *Phthirius pubis* Two species of pediculi were formerly recognized but since they interbreed freely only one species is now recognized *P humanus* and the body louse and head louse are considered varieties *P humanus (capitis)* and *P humanus (vestimenti)* of this species The former lives upon the scalp and attaches its eggs commonly called ' nit to the hair The latter lives in the clothing and deposits its eggs there

As the result of the irritation arising from louse bites more or less serious conditions arise (Moore and Hirschfelder[12] Nuttall[13]) Pustules and crusts may be formed in the scalp and the cervical lymph nodes become enlarged Eczematous processes may also appear and extend over the face and other parts of the body Blepharitis and conjunctivitis are frequently associated with head lice As the result of the bites of body lice more or less scratching is indulged in which produces rather characteristically distributed excoriations and lesions resulting therefrom In neglected cases the condition is serious in fact

many individuals distinguished in the history of the world are said to have died eventually of louse disease

Pediculi — *Pediculus humanus* transmits the following diseases typhus relapsing fever (North African and European types) and trench fever In the case of typhus the louse does not become infectious until eight or ten days after biting a typhus patient Either the excrement or the crushed louse scratched into the skin produces infection (Nicolle Comte and Conseil[14]) This is also the case in the transmission of relapsing fever The virus of this disease may be transmitted through several generations of lice In the case of trench fever infection may follow the bite of infected lice the usual manner of infection or by the inoculation of the skin with louse excrement in the process of scratching The virus of this latter disease is said to be filterable (Trench Fever Report of Commission of American Red Cross Research Committee[15])

Fleas — Fleas *Siphonaptera* are wingless insects more or less related to and sometimes classified with the *Diptera* or two winged flies Their flat bodies enable them to pass through the fur of animals which they infest and the development of their posterior pair of limbs enables them to make phenomenal leaps The eggs are large and are deposited in the fur of the animal upon which they live or in the shed fur and rubbish of animal haunts The eggs of the human flea for example are distributed in dust and debris in the cracks of floors etc The larvæ are maggot like and feed upon bits of organic material especially dried blood found in the shed fur of infested animals After a period of growth they enter upon the pupal stage and spin a cocoon Being voracious feeders the adults of some species die very quickly on removal from their host others live for long periods especially when protected by dust and rubbish at low temperatures The various species of fleas are associated with definite hosts but many feed to a large extent as the occasion affords on other than their normal host During feeding undigested blood in considerable quantity may pass through the alimentary tract and such dejecta drying upon hair or fur serve as food for larval fleas

The rat flea *Xenopsylla cheopsis* is probably the most important agent in the transmission of bubonic plague *Bacillus pestis* multiplies rapidly in the alimentary tract of this species and it is said that infected fleas are abnormally active moving from place to place rather than gorging themselves at one spot It is quite generally conceded that infection of the human being is usually accomplished by the inoculation of the skin with the excrement of the flea through scratching or rubbing It is a notable fact that cleanly habits especially the daily bath greatly diminish the chances of infection even though the individual may be exposed to infected fleas It is said however that the growth of bacilli in infected fleas produces more or less obstruction of the alimentary tract so that infectious material may be regurgitated into the bite wound Other species that

attack both man and susceptible animals may serve to transmit the disease Thus the human flea *Pulex irritans*, the European rat flea, *Ceratophyllus fasciatus*, and in California the squirrel fleas, *Hoplopsyllus anomalos* and *Ceratophyllus acutus* have been shown to carry the infection

Various measures are employed in destroying fleas, as the destruction of animals serving as hosts cleanliness of apartments, filling of cracks, the use of naphthalene or fumigation Sodium fluoride scattered about in powder form is very effective Water is especially effective in the prevention of the breeding of fleas and by the daily use of the hose, kennels and animals quarters may be kept comparatively free of these pests

Chigger or Sand Flea — The Chigger "Jigger," or sand flea *Dermatophilus penetrans*, attacks a variety of hosts but especially the human being and the pig The impregnated female burrows into the skin, more especially about the toes and then becomes greatly distended with eggs so that she may approach the size of a pea The two posterior segments of the body plug the opening made in the skin so that the eggs are discharged on the surface The larvæ develop in dry sandy soil Proper footwear and leggings prevent to a large extent the attacks of this flea

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CHAPTER XL A

ARACHNIDISM

By Frederick R Taylor

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Definition —Arachnidism is the term commonly applied to the effects of the bites of venomous spiders Zoologically the term is too inclusive for the *Arachnida* include scorpions pseudoscorpions ticks mites etc in addition to spiders Some taxonomists include also king crabs while others do not

Spiders comprise the subgroup of arachnids known as *Araneida*, so araneidism would be the zoollogically preferable term for the effects of their bites in man Etymologically however Arachnida is derived

from Arachne, a mythological Lydian maiden who presumed to vie with Minerva in weaving and embroidery Minerva punished her for this sacrilege by turning her into a spider

In this chapter the writer will avoid confusion by dealing with spider bites, scorpion stings etc as such, although articles in the Bibliography entitled Arachnidism" invariably refer to spider bites The pseudoscorpions or book scorpions and the king crabs require no consideration here, as they do not attack man A formidable arachnid resembling a spider but with scorpion like claws in front, the *Galeodes* will be mentioned here

SPIDER BITES

Introduction

Many conflicting views have been held on spider bites Lay viewpoints run from morbid horror to utter contempt In the past 25 years much scientific interest has been taken in the subject, and a number of spiders significantly harmful to man have been discussed in the literature

History

According to Cohen the *Susruta Samhita*, written in India somewhere between 1000 and 600 B C, tells of spider bites fatal within a week and mentions 16 kinds of spiders, 8 of which cause fatal bites, and 8 of which cause bites curable with difficulty It states that the Chinese considered the black spider as one of the five poisons", the other four being the toad snake scorpion and centipede However, no species of *Latrodectus* is described in any surely recognizable way

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clusion being that there is no doubt that the spiders of this genus *Latrodectus* are very poisonous and that their bite has been followed by severe illness and in some cases death

Alexander quotes as follows from The Indian Doctor s Dispensatory being Father Smith s Advice Respecting Diseases and their Cure by Peter Smith of Miami County Ohio printed by Browne and Locker Cincinnati Ohio 1812 reprint 1901 by J U and C G Lloyd Cincinnati (p 74 of reprint) How important must it be to be able to cure the bite or sting of serpents or spiders *especially the black spider with a red spot on his back* called the tarantula so common and so dreadful in southern climates, "

In 1926 the paper of Emil Bogen then a resident physician at the Los Angeles General Hospital on arachnidism which won the California Medical Association prize for that year received wide professional publicity and recognition and finally established black widow spider bite as a definite clinical entity

Latrodectus Genus of Spiders

The largest spiders are rarely the most dangerous to man Indeed with the possible exception of *Atrax robustus* in Australia to be mentioned later the most dangerous spiders throughout the world belong to the genus *Latrodectus* Scores of species have been described but as there is some overlapping in the nomenclature and as it is probable that many supposedly distinct species in various parts of the world are identical with those having different names elsewhere only a few of the more important ones will be mentioned *Latrodectus tredecim guttatus* and *L malmignattus* are important in Europe *L concinnus* and *L indistinctus* are found in South Africa and *L menavodi* inhabit Madagascar *L hasseltii* has a wide range being found in Australia New Zealand a large part of Asia and certain Pacific islands In New Zealand it is called the katipo spider in the Philippines the red back spider while in Australia it is known as the venomous spider jockey spider red striped or red back spider Its distinguishing characteristic is its orange or reddish longitudinal stripe on the dorsal surface of the abdominal segment tapering to a point at the rear the general body color being dark gray *L lugubris* as well as *L tredecim guttatus* is found in Palestine

In general there seems to be little if any difference in the effect-

from Arachne, a mythological Lydian maiden who presumed to vie with Minerva in weaving and embroidery Minerva punished her for this sacrilege by turning her into a spider

In this chapter the writer will avoid confusion by dealing with spider bites, scorpion stings etc as such, although articles in the Bibliography entitled 'Arachnidism" invariably refer to spider bites The pseudoscorpions or book scorpions and the king crabs require no consideration here, as they do not attack man A formidable arachnid resembling a spider but with scorpion-like claws in front, the *Galeodes*, will be mentioned here

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of the bites of the various species of *Latrodectus* Occasionally some author has claimed that one species causes less severe symptoms than another but even with the same individual spider the effects vary greatly according to the degree of the bite and the amount of venom injected The spider does not always inject all the venom available, and at times as when it has recently bitten another victim and emptied its venom sacs but little venom may be available

Latrodectus Mactans—The one venomous spider of great importance in the United States is the *Latrodectus mactans* Another closely related species *L geometricus*, occurs in southern Florida

The word, Latrodectus is said to come from the Greek λατρο, "robber", and Δεκτω 'bite'—"robber-biter" Mactans means "murderous' Some derive the name from similar words meaning "pay received

Latrodectus mactans has many common names, among which may be listed 'black widow', "shoe-button spider", hour glass spider, "red spotted spider' 'T spider", 'red rump', 'poison lady", black spider' 'ebony spider' long legged spider' "southern spider' and 'deadly spider' In certain American Indian dialects it is known as 'pok o-moo and chintatlahue In Mexico it is called 'araña capulina" (cherry spider) In Chile it is known as "araña del trigo" It is called 'black widow from the supposition that the female eats the male immediately after mating As a matter of fact this is not the rule but does occur when the female is in dire hunger and it may occur also, if the male attempts to mate prematurely Blair states that the life span of the female is about 1 year that of the male usually less Skinner says that the young spiders are cannibalistic the weak ones being devoured by the stronger ones in the same brood According to Vail the females have been known to kill and eat one another Thorp and Woodson state that in the immature male the venom glands have only from about ¼ to 1/3 the capacity of those of the immature female, and as the spiders mature the glands of the male atrophy whereas those of the female increase in size thus explaining the harmlessness of the male to man

The female *L mactans* is glossy black with a body about half an inch long The abdominal segment resembles a shoe button On the ventral surface is a scarlet spot shaped like an hour glass with flat ends (Fig 1) Occasional variants show 2 or 3 red dots or none at all in place of the hour glass mark Other inconstant red and yellow markings may occur Some excellent color plates of this, as well as of a number

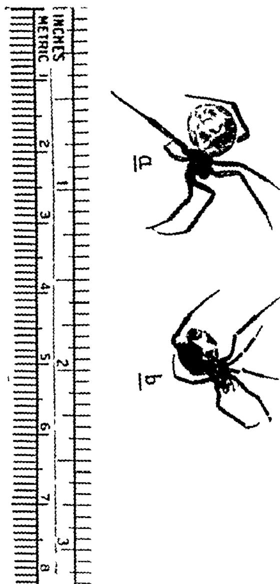


Fig 1 Two female black widow spiders (Latrodectus mactans) X 1 *a* Dorsal view *b* Ventral view The abdominal segment in *a* has been bleached somewhat from its original glossy black by the alcohol used as preserving fluid The hour glass mark in *b* was originally bright scarlet Other markings contrasting with the black were originally either yellow or scarlet

of other spiders, may be found in the August, 1933 number of the *National Geographic Magazine*.

The Venom.—Troise reports that the venom of the *Latrodectus* has the character of a toxin, is destroyed at 70° C and stimulates the formation of an antitoxin. Hall and Vogelsang state that it is a non hemolytic neurotoxin. D'Amour and his associates have shown that the venom is a protein, probably a toxalbumin, which, weight for weight, is about 15 times as toxic as rattlesnake venom. The effects in man are due largely to its property of causing violent muscle spasms. Palmer cites Dr T J Turpin of Esmeralda, Mexico, as saying that he never felt himself more in danger of death than during the 2 days he was ill from the bite of a *Latrodectus*. A physician of the present writer's acquaintance, who was bitten as a boy, stated that he felt as if every muscle in his body were being torn loose from its insertion. Palmer, quoting Coleman, says that the macerated poison glands of one female *L mactans*, mixed with distilled water, were injected into a cat. In about 5 minutes clonic convulsions appeared, followed by tonic spasm and in 10 minutes the cat was dead. Another cat died in about 3 minutes and a rabbit in 2½ minutes. Palmer also says that Coleman took repeated minute doses by mouth and in 3 days developed slow pulse, slight fever, severe headache, dilated pupils, clonic spasms of the muscles of the chest and abdomen and marked distress about the heart with pains radiating to the left elbow suggesting angina pectoris. His bowels did not move for 2 days. The venom has been used as arrow poison by certain American Indian tribes, sometimes mixed with rattlesnake venom.

Sampayo has made an exhaustive pharmacodynamic study of the venom and concludes that it contains a neurotoxic substance with a diffuse excitatory action throughout the entire central nervous system, also involving the autonomic nervous system and raising arterial pressure by generalized vasoconstriction, even after removal of the adrenals, kidneys and other abdominal viscera and after decerebration and extirpation of the carotid sinuses and both vagi. It did not increase adrenalin secretion or affect the involuntary muscles of the bronchioles, intestines or uterus. Respiratory difficulties were due to thoracic and abdominal muscular spasms. Repetition of dosage was without pharmacologic effect. Intravenous injection of antitoxic serum prevented or abolished the toxic effects of the venom.

Pirosky, Sampayo and Franceschi immunized a horse by subcutaneous injection of cephalothoraces of *L mactans*. The specific antitoxin thus obtained was purified by Pope's method with a purification index

of 6 One c c of this antitoxin protected 50 per cent of a series of white mice against 3 000 minimal lethal doses and 1 gram of protein would protect against 49 584 such doses of the venom

Thorp and Woodson state that Coleman found the eggs of the black widow to be poisonous Later Blair found that 2 eggs crushed and emulsified in a drop of saline solution would kill an adult white mouse when injected intraperitoneally A few drops of a saline emulsion of eggs killed a rabbit in 2 minutes

Very few necropsies have been reported in man in cases of spider bite and no characteristic changes have been noted In one case Beasley could find no gross pathological changes that could account for the patient s death but noted the existence of acute hemorrhagic nephritis Hall and Vogelsang found the necrosis in the liver, kidneys, spleen and adrenals of animals killed with the venom

Recovery from one bite is said to establish some degree of immunity Ellis reported the case of a patient who was bitten twice 2 weeks apart only slightly the first time more severely the second whose symptoms lasted only 3 or 4 hours the first time and even less the second However Hargis says that immunity is not lasting

Distribution and Incidence

The habitat of *L mactans* in the Western Hemisphere ranges from Canada to Tierra del Fuego In the United States bites are far more frequent in the southwestern southeastern south central and Rocky Mountain states than elsewhere Thorp and Woodson have collected reports of 1 291 cases of black widow spider bite in the United States from 1726 to 1943 California is far ahead of any other state in the number of cases reported during that period 578 Virginia coming next with 173 cases and Florida third with 126 cases No other state had reported over 71 cases North Carolina according to Thorp and Woodson had recorded only 34 cases in these 217 years The condition however is very much more common in this state than the published reports would indicate for most cases occur in more or less isolated sections where physicians are few and have little time or inclination to write whereas many authors of great clinical experience in urban centers have never seen a case When about 10 cases had been reported from North Carolina a general discussion of a paper on black widow spider bite before the medical society of that state brought out statements from

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Symptomatology

Four phases may be recognized in black widow poisoning the moment of the bite, a quiescent period an acute phase and convalescence At the moment of the bite there is rarely much immediate discomfort from the bite The patient may not know he has been bitten but usually there is a sharp momentary prick If discomfort persists it is less severe than a bee sting Swelling is very rare A *quiescent period* now ensues, lasting from a couple of minutes to half an hour, rarely prolonged to 3 hours or more

Blair experimented on himself, causing a black widow to bite him on the finger, and has given us the classical description of the symptomatology Within about [illegible] minutes an area of blanching developed about the bite, accompanied by a burning sensation Beyond the area of blanching the finger was reddened The pain gradually extended up his arm thus ushering in the acute phase, and then became disseminated over his body

Blair recognizes 3 stages in the *acute phase*, the stage of *lymphatic absorption*, in which the pain spreads along the course of the lymphatic drainage of the area of the bite the stage of *vascular dissemination* of the venom in which generalized pain and a certain amount of shock occur and the stage of *elimination*, in which hypertension diaphoresis decreasing muscular pains slight fever a neutrophilic leukocytosis of varying degree albuminuria with a few red cells and casts in the urine headache edema of the face and ankles and other evidences of acute nephritis may occur

In the cases observed by the present author the acute period has been ushered in by the development of severe pains around the bite which spread quickly over the body They become agonizing and tend to develop maximal intensity in the abdomen where a striking clinical picture appears, suggesting some major abdominal catastrophe such as a ruptured viscus Tenderness may be absent When present it is generalized Noland emphasizes the disproportion between the great pain and the slight tenderness When present the latter tends to disappear before the pain Most remarkable of all is the abdominal rigidity At times it is greater than the present writer has ever seen in any other condition A few cases without abdominal rigidity have been reported Cases have been operated on by mistake for grave surgical emergencies

Usually there is a generalized but incoordinated muscular rigidity throughout the whole body The patient, wild with pain, tosses about

many physicians practicing in rural sections, who rarely published medical papers, to the effect that they had individually treated dozens or even scores of cases That the condition is by no means restricted to rural areas however, is shown by the warning sounded in 1934 by Becker and D Amour of Denver that *L mactans* seemed to be invading cities of considerable size, being found in garages, basements, sheds under steps and around window sills, porches, etc By 1937 the spider had been found in every state in the Union, and by 1943 bites had been reported from 32 states

An anonymous article in the Public Health Reports of the United States Public Health Service records the heavy infestation of a ship with black widow spiders, 174 being killed in the first fumigation with hydrocyanic acid gas Tobar reported 23 cases of black widow spider bite which he observed personally A very large number of cases have been reported from Argentina, Sampayo alone having reported about 300 cases The extent of his work may be partially realized from the fact that he experimented with no less than 12 000 spiders of the *L mactans* species and also with *L geometricus* Ellis described an "epidemic" of black widow bites in eastern Arkansas He saw no cases during his first 30 years of general practice, then 5 cases within a very short time He mentioned similar virtual epidemics in New Zealand Australia and Madagascar A considerable number of cases occurred among soldiers in training camps in the United States during World War II

Thorp and Woodson state in their book that in Sardinia great epidemics of black widow bites occurred in 1833 and again in 1839, when man cattle and other domestic animals fell victims to this spider They cite also a lore developed by certain Peruvian Indians to the effect that *Latrodectus* comes at stated periods as an inevitable plague and that little can be done to stave off such depredations According to the same authors in 1838 and 1839 the nomadic tribes of southern Russia lost great numbers of cattle from *Latrodectus* bite, and there were many human victims At this time children and older persons were employed to search the fields and meadows and kill the creatures The same authors quote a news account of the discovery of a gigantic black widow breeding ground covering several acres and harboring thousands of the spiders where a parade ground was being graded at a naval station Wholesale destruction of the spiders was accomplished by flame throwers

diagnostic problem that exists when one is unfamiliar with the condition especially if an intelligent history cannot be obtained and some extraneous factor such as hernia peptic ulcer, etc exists A 68 year old rather mentally defective man with obvious arteriosclerosis while sitting on a privy seat was bitten on the penis about 9 P M He had some local pain until about midnight when he got worse The writer saw him about 1 A M The patient insisted that a snake had bitten him but admitted that he had seen no snake There was no swelling and no mark of a bite was found He had had an incomplete right inguinal hernia for 30 years which had suddenly become very painful He also had extreme general abdominal pain with some tenderness and the greatest abdominal rigidity the author has ever felt There was no nausea or vomiting A surgical consultant was called As the picture seemed atypical we looked further for a bite Finally we found a very slight red place on the prepuce such as chafing clothing might make We then inspected the privy We saw no snakes or spiders but coarse irregular webs were all about the seat On returning to the patient his rectum was partially prolapsed We reduced this without relief The temperature was subnormal and the pulse rate 9 per minute Because of the absence of shock we finally agreed upon a tentative diagnosis of spider bite although we had seen or heard of nothing like it before Half a grain of morphine sulfate was given hypodermically At 8 A M his temperature was 97 F pulse 86 and of good quality respiration quiet blood pressure 160/1- He felt better but still had great abdominal rigidity although the tenderness had entirely disappeared His urine showed only a faint trace of albumin and a few hyaline casts Red white and differential blood counts were normal The patient now complained of dyspnea and tingling in his feet He was excited and thought he was dying His heart sounds were a little weak and his tendon reflexes greatly increased especially the patellar Neurological findings otherwise were normal The tingling feet and increased knee jerks persisted next day Nine days later all symptoms except the increased reflexes had disappeared

Hilton reports the case of a woman 8 months pregnant who was bitten by a black widow in whom the symptoms were mistaken for those of premature separation of the placenta She recovered and was delivered at term of a healthy baby

Shields has reported the case of a man bitten behind the right ear by a black spider of unknown type with resulting paralysis of that side of the face involving all , branches of the 7th nerve with subsequent

cries out, catches his breath in irregular gasps and often says that he is dying Moderate fever, 100° to 102° F, and a neutrophilic leukocytosis of varying degree usually are present, but the temperature may be subnormal and the blood count normal Beasley's fatal case had a white count of 35,100 with 86 per cent neutrophiles and a subnormal temperature Sweating may be profuse The pulse rarely is fast, despite the great restlessness, bradycardia may occur The blood pressure is somewhat raised The heart sounds may be rather weak The tendon reflexes are greatly increased This may persist long after other symptoms disappear The spinal fluid has been found under increased pressure but otherwise normal General or local numbness and tingling occur Widespread muscular twitchings are the rule Nausea and vomiting are common, as is retention of urine

Many inconstant symptoms are described such as cyanosis, edema of eyelids, transient paralyses, convulsions, local clonic or tonic spasms scarlatiniform eruptions, tremors chills, vertigo, jaundice and priapism One case has been described which resembled tetanus Beasley's patient, a 16 year old boy, had a convulsion 30 minutes before death Vail reported 2 cases with profuse lacrimation Shock has been observed although in the present writer's experience it has never been equal to that characteristic of a ruptured viscus He regards the absence of extreme shock, indeed, as an important diagnostic point However, he has never seen a fatal case Walker described a case of *Latrodectus* spider bite in Madagascar showing a cold sweat limited to the right side of the body from the waist down The location of the bite was not stated Hagan mentioned finding an enlarged liver which he considered merely a part of a generalized engorgement of the viscera with blood

During *convalescence* the striking findings are prostration and hyperactive tendon reflexes, usually lasting from a few days to a few weeks One patient described by Noon and Minear who had been bitten on the index finger of his right hand later developed a rheumatic ache in his right shoulder lasting several months and stated a year afterwards that he still felt nervous and never felt sure of himself on horseback as he had done before the bite Klein noted late mental symptoms such as inability to remember familiar faces, events names and spelling of words, also sensitiveness to noises, so that a telephone bell sounded like a fire gong, etc Walsh reported the case of a patient who, after being bitten, was delirious when admitted to the hospital, but who after recovery had little or no memory of the experience

The present author's first case, seen in 1915, will illustrate the

have been due to unwise treatment, e g, the use of very large doses of alcohol so often falsely thought by the laity to be the proper treatment for snake bite and by analogy for spider bite Children are very susceptible to alcohol and may succumb to large doses Apoplexy has occurred in some cases notably in the elderly presumably due to the rise in blood pressure rupturing sclerotic vessels Cornwell reported a fatal case complicated by erysipelas and Thorp and Woodson mention one in a physician due to septicemia produced by the bite

Treatment

Although the present author has never had the opportunity to use it evidence seems to be accumulating that in areas where *Latrodectus* bite is very common a specific antivenin should be available as it appears to be the most effective treatment known Its use is especially indicated in children the aged etc in whom a relatively high mortality may be expected Kirby Smith found relief much more prompt with antivenin therapy and reported an almost universal recurrence of pain 4 or 5 days after the usual drug treatment in his hands but this did not occur in a series of patients treated with specific antivenin The present writer however has not noted such recurrences after the usual drug treatment In many cases antivenin is not available promptly and the emergency demands immediate action Fortunately drugs usually are adequate and are of course preferable in serum sensitive patients The usual treatment with drugs is as follows

1 Morphine sulfate 15 mgm (1/4 gr) and atropine sulfate 0 4 mgm (1/150 gr) hypodermically at once and repeated as needed

Ten c c of a 10 per cent solution of calcium gluconate intravenously A 20 per cent solution may be used if preferred but care must be taken not to let this irritating solution escape from the vein Vail however warns against the use of calcium intravenously in digitalized patients as it may be fatal to them In such cases antivenin therapy or another type of drug treatment should be used

3 A simple cleansing enema

4 Immersion of the patient in a hot bath seems to have a very helpful effect in relaxing some of the muscle spasm

5 If the above measures fail to give adequate relief or if calcium is contraindicated 10 c c of a 25 per cent solution of magnesium sulfate may be given intravenously This should be given slowly and

recovery The present writer has seen the same thing follow a wasp sting in a facial nerve just as it emerged from the stylomastoid foramen

Diagnosis

The central thing is the history of a bite, but this may be unobtainable It is essential to distinguish black widow bite from an abdominal surgical emergency The history of a bite, when obtainable the mark of a bite when visible, usually, but not always the lack of any known abdominal condition such as peptic ulcer with its risk of perforation or hernia with its risk of strangulation, the relative rarity of spider bite in the female, the frequency of bites while using an outdoor privy, the lack of extreme shock or of very rapid pulse, the general character of the abdominal pain and rigidity with no localizing points, the numbness and tingling of various parts of the body, the increase of tendon reflexes the extra-abdominal muscle spasms, clonic or tonic, the occasional presence of convulsions or of a scarlatiniform rash, and, if perforation of a viscus is to be differentiated the lack of a gas bubble in the peritoneal cavity as shown by x ray, all favor the diagnosis of spider bite Acute pancreatitis, mesenteric thrombosis, coronary occlusion with abdominal symptoms, dissecting aneurism, the abdominal crises of tabes etc must be excluded also by proper consideration along with a search for the characteristic features of such conditions

To think of spider bite is to make the diagnosis in most cases Even where a chronic condition predisposing to perforation of a viscus strangulation, etc occurs the widespread symptoms outside the abdomen should be decisive Every patient with extreme abdominal rigidity should be questioned regarding the possibility of spider bite

Prognosis

In the 1 291 cases collected by Thorp and Woodson there were 55 deaths a mortality rate of about 4 26 per cent The present author feels sure that this is a higher mortality than actually exists in general for the reason that a very much larger proportion of fatal cases is reported than of non fatal He believes that the actual mortality is not over 2 per cent and may be less than that Vaughan says that most deaths have been in children Bogen suggested years ago that some deaths may

quently and outbuildings as well as dwelling houses should be screened adequately Enemies of the spider, such as birds harmless reptiles insects etc should be encouraged Among these the common mud dauber wasp may be mentioned as of special value as it seems to be an arch enemy of the black widow In California Cowles found that the San Diego lizard *Gerrhonotus multicarinatus*, is of special value in destroying the spider and urged its protection Bogen and Loomis advise wearing white gloves and clothing a large white hat a collar turned up at the neck and trouser legs closed at the bottom while working around the spiders The white clothing is to make the black spider instantly visible Boiling water or steam effectively destroys the spiders For small boxes, chests etc ordinary naphthalene moth balls are helpful Sulfur dioxide fumigation is useful in larger spaces such as rooms if they can be properly sealed using a pound of sulfur for every 1 000 cubic feet of space and fumigating for at least one hour In special cases where it is safe cyanide fumigation by experts may be employed

Bogen and Loomis stated some years ago that for open spaces such as outdoor privies spaces under houses etc, nothing reliable had been found so far although creosote spraying had been advised This appears to be true still DDT as ordinarily used seems to be ineffective against spiders (personal communication from F C Bishopp of the U S Department of Agriculture) Direct spraying of the spider with kerosene or still better kerosene to which from 1 to 10 per cent of isoamyl alcohol has been added is effective but spraying the web is useless Fire hazards must be considered in using such preparations as well as their effects on paints finishes etc Mechanical methods of cleaning out webs rubbish etc and of killing the spiders are in general the most effective It should be remembered that for every species of spider harmful to man there are hundreds of great value in controlling insect pests The latter should be protected so long as they do not intrude into undesirable locations

Other Spiders

The widespread fear of the tarantulas of the southwestern United States seems largely unfounded They belong to various genera of the family *Aviculariidae* (see Vol V Chap XL of this work) A personal communication from Dr R E McBride of Las Cruces New Mexico received some years ago stated that in 30 years practice where tarantulas abound he had never seen a person who claimed to have been bitten

the patient watched for signs of respiratory depression during, and for some time after, the injection. Vail considers 10 c c of a 10 per cent solution of magnesium sulfate in 50 c c of 50 per cent glucose superior to magnesium sulfate alone. The present writer has not tried this.

6. If preferred, a soluble barbiturate with a fairly prolonged action may be given intravenously, using a solution containing 0.1 gm per c c, not giving over 1 c c a minute, stopping as soon as the effects of the drug become evident and in no case giving over 10 c c of such a solution at one dose. Usually the patient will fall asleep before the 10 c c has been completely given. This indicates immediate cessation of administration of the drug. After such treatment the patient should be watched just as one watches a patient recovering from general anesthesia, pushing the jaw forward, if the tongue falls back in the throat, etc, and using artificial respiration, if needed.

7. Bell and Boone report a patient who did not respond to calcium gluconate and sedatives for 5½ hours, who obtained dramatic relief 1 hour after the intramuscular injection of 2 c c of a 1 ,000 solution of neostigmine methyl sulfate with 0.4 mg (1/150 gr) of atropine sulfate.

Drastic local treatment, such as incision at the site of the bite, cauterization or local injection of supposed antidotes, has been condemned by Bogen as useless and predisposing to secondary infection. The simple application of some antiseptic such as tincture of metaphen may be used. If a bite on a limb is seen immediately, the intermittent application of a tourniquet with free local incision might seem rational, but bites are seldom on a limb, and a physician seldom sees a case immediately. Incision of the genitals, where most bites occur, is, of course contraindicated. Alcohol internally is useless. Retention of urine and constipation must be relieved by catheterization and enemata. Robinson reported a case with acute urinary retention that was not relieved by morphine or intravenous glucose but was by lumbar puncture. Calcium and magnesium were not given.

Prophylaxis

The public must be taught to know the *L. mactans*, to kill it wherever it is found and to seek and destroy its webs especially in privies, cellars, attics, barns, garages, woodpiles, closets, etc. Outdoor privy seats should be hinged so that their under surfaces can be inspected fre

strong electric shocks in his tongue lips the base of his nose and cheeks He described his face as feeling like a boil ready to burst and like a limb gone to sleep This was followed by depression and lacrimation It was hard for him to control his eyelids he became nauseated felt choked and his nasal passages were obstructed His vision became dim several images of a single object would merge into one another and he had difficulty in using his hands and feet In a few hours the tingling extended to his hips shoulders and back and he belched and sneezed considerably The last two symptoms had disappeared by the next day but a tingling sensation on exposure to cold remained and on the 3rd day his foot was sore On the 4th day his only symptoms were drowsiness and fatigue His teeth and jaws had ached throughout the acute period of his illness and sensation had been lost on the front and sides of his chest He made an uneventful recovery No special treatment was suggested

Glyptocranium gasterocanthoides is a venomous Peruvian spider often found on vines being pruned looking like a bud on such a vine It rarely spins webs depending on its protective mimicry of buds Extensive necrosis and sloughing may follow its bite

Schmaus reports a case of poisoning from a little known spider *Loxosceles refescens* Gotten and MacGowan report hemoglobinuria from the bite of the spider *Amaurobius ferox* Skinner mentions a spider in Panama *Sericopelma communis* causing severe local symptoms at the site of the bite and in neighboring joints such as swelling redness and pain lasting about a week

The *mygales* are large hairy spiders usually more frightful looking than dangerous The bites of the mygales of southern Europe such as *Ctenus sauvagei*, cause local lesions of little gravity but the bite of a Brazilian mygale of the genus *Phormictopus* cause violent pains blisters fever tachycardia hematuria jaundice and death in 4 days in a healthy 30 year old woman

The largest spiders in the world are in South America and belong to the genus *Therasophides* according to Thorp and Woodson They are closely related to the tarantulas of the United States Their bodies may grow to a length of 3½ inches and according to Thorp and Woodson their bites cause edema necrosis anesthesia and paralysis of the bitten member

Severe local lesions as produced by some of the larger spiders usually are phlegmonous or gangrenous in character General symptoms are of two types hemolytic with special effect on the hepatic and

by one However, citing Bull 83, Arizona State Experiment Station, Tucson, he pointed out that 4 or 5 patients had shown severe symptoms such as local swelling, blueness hemorrhage, sloughing, etc followed by indolent ulcers Culpeper's observations also suggest some danger in ignoring tarantulas entirely, but serious trouble from them is rare Thorp and Woodson cite instances in which half an hour of teasing has been required to make them bite man They also state that various "tarantulas", in the loose sense of large hairy spiders of any sort, occur throughout Africa, Central America, Haiti, San Domingo, Java and elsewhere

The true European tarantula, *Lycosa tarantula*, a wolf spider, is the largest European spider While active and quick, it is not particularly aggressive Outbreaks of uncontrollable dancing following its bites have been hysterical not toxic, manifestations The *Lycosa singoriensis* or *infernalis* of southern Russia creates a serious problem where it exists in large numbers, for it may attack and kill great numbers of domestic animals The bite of *Lycosa raptoria* of South America may cause dry gangrene

Thorp and Woodson state that the giant crab spiders belonging to the family *Heteropodidae*, often found in bunches of bananas, can inflict painful bites with marked local swelling They further say that 2 species of spiders in Australia *Atrax formidabilis* and *A robustus*, which, although popularly called trap-door spiders, are really funnel-web spiders, have caused very severe pain by their bites, and *A robustus* has been credited with several deaths Both sexes of the latter bite *A formidabilis* is larger than *A robustus*, and only the male seems to be known

Upham and Klein note that the bite of *A formidabilis* causes delirium shivering and profuse salivation bronchial secretion and sweating There is intense pain in the region of the bite followed by numbness The surface veins become distended with dark blood Eight hours after the bite they observed severe vomiting and cramps in the limbs and abdominal muscles The patient had a frightened anxious look The pulse was weak and its rate 60 per minute Respiration was labored The pupils were contracted

The same authors describe in detail the striking case of the bite of *A robustus* in a patient of high intelligence (he had an LL D degree) Their findings may be summarized as follows The patient bitten on his toe at the moment merely felt pain like a bee sting Then listing his symptoms in the general order of their appearance his tongue became numb he lost the sense of taste and he had sensations resembling

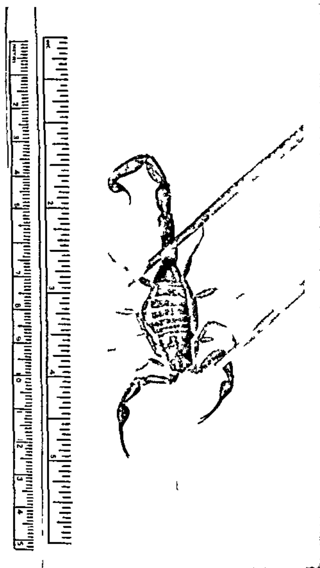


Fig 2 Live scorpion held down with forceps It was imported in a bunch of bananas to Durham N C The banana dealer was stung by it and went to Duke Hospital for treatment where Dr David Cayer made the photograph

renal parenchyma, and neuromuscular The *Ctenus* of South America has a tetanizing venom

In severe bites from these larger spiders, if a specific antivenin be available, it should be used Otherwise the treatment is symptomatic Local lesions should be treated on surgical principles

GALEODES

Galeodes is the name given to a genus of large hairy, active, rapacious spider-like arachnids of the order *Solpugida*, found in the warmer parts of the world They lack the constricted waist of the true spiders and differ from them in many other ways The Arabs call them 'dancing spiders' or scorpions of the wind Their chelicerae form pincers like those of scorpions but otherwise they have little resemblance to them, lacking the tail armed with a sting Apparently it has not been proved that they have venom glands Opinions regarding their bites are very contradictory They are not feared in Morocco or Kenya, but are dreaded in West Africa, southern Russia, in the Asiatic steppes and in India Where they are abundant they enter tents at night and bite sleeping men and beasts The results of their bites sometimes serious probably are due to secondary infection in the multiple wounds they make Treatment is on surgical principles

SCORPION STINGS

Scorpions have 4 pairs of legs and are armed with 2 chelicerae or anterior pincers analogous to those of crabs lobsters and crawfish Their abdominal segments are prolonged by a sort of jointed tail, the distal segment of which, or telson, is tipped by a sharp, curved needle like sting with which they inoculate their venom (Fig 2) They vary in length from about ½ to 6 inches from the head to the tip of the long tail and in color from pale yellow through brown to black There are various classifications of scorpions showing well over 100 species They may have 6, 8 10 or 12 eyes The tail can be raised in the arc of a circle in such a way as to sting the prey which is held in the chelicerae When a scorpion is annoyed or trying to defend itself as when it is surrounded by a circle of glowing coals, it will furiously go through the motions of stinging and may seem to sting itself This has given rise to the legend of scorpion suicide under such conditions, but the scorpion does not really sting itself and if it did it would do little harm, as it is immune to its own venom

Distribution and Incidence

Scorpions are widely distributed throughout the tropical subtropical and desert regions of the world While they are not very aggressive their stings are frequent as certain species become more or less domesticated, getting into human dwellings and even into bedding and clothing

Symptomatology

All scorpions are venomous although the effects of their stings vary from relatively brief severe local pain to death In general the larger scorpions are more dangerous than the small ones although there is no fixed ratio between size and toxicity certain species being especially deadly which are no larger than others much less so As a boy the present author was stung on a toe by a small pale yellow scorpion in a mountain camp in southern California For about an hour the toe felt as if a burning match were being held under it and it became red and swelled slightly but there were no constitutional symptoms and in a few hours the local ones had practically disappeared without treatment Fretz of Trinidad where scorpions abound mentions 2 kinds on that island a small brown one and a large black one the former relatively harmless but the latter extremely toxic and dangerous to both children and adults The constitutional symptoms of the latter begin to develop about $\frac{1}{2}$ to 1 hour after the sting the earliest of them being dyspnea and muscular contractions Later the patient goes into extreme shock with cold clammy sweats profuse frothy vomiting slow thin pulse and subnormal temperature This critical period lasts about 3 hours Then the patient who is to recover begins to improve and recovery is practically complete within 24 hours Death rarely ensues Epileptiform convulsions may occur Albuminuria usually is absent In 12 out of 14 cases studied by Fretz a transient glycosuria developed which lasted from 2 to 5 days In 3 cases the maximum percentages of glucose recorded in the urine were 0 64 0 41 and 0 4 respectively

Lang reported a case of scorpion sting of a severity previously unknown in Baitalpur Central Provinces India where stings are common A man about 22 years old was stung on his left great toe An over zealous person put a rope tourniquet around his left foot The patient arrived for treatment 15 minutes after the sting complaining of great pain and general weakness his skin being cold and clammy and show

Extensive studies of South American scorpions have been made at the Bello Horizonte branch of the Instituto Oswaldo Cruz and of North African species at the Pasteur Institute of Algeria At the former institution De Mello Campos collected several thousand live and dead scorpions and caudal vesicles of the species *Tityus bahiensis* and *T serrulatus* In 1920 circulars were sent out widely among parish priests, presidents of municipalities and consular and diplomatic agents abroad requesting scorpions for taxonomic and other purposes resulting in abundant world-wide material In addition to all this, De Mello Campos studied the material at the central Instituto Oswaldo Cruz in Rio de Janeiro and in various other museums having scorpion collections

The *venom* is a clear liquid which on being expelled, quickly becomes cloudy and filled with granules, according to Roch It does not penetrate healthy unbroken skin and is destroyed by the digestive juices De Magalhaes in Bello Horizonte studied the action of the venom of 3 species of scorpions of the genus *Tityus* and 16 640 individual specimens of the genus *Botryrurus*, testing the action of the venom on 97 species of living creatures from *Chlamydozoa* to man He found that the effects decreased in severity according to the method of introduction intracerebral being the most severe, then intracerebellar intracardiac intravenous intraperitoneal, intramuscular and subcutaneous, in descending order

Dey states that the neurotoxin in Indian species observed by him acts on the respiratory and vasomotor centers and also on the nerve terminals and end plates of both striped and unstriped muscle and that the venom also contains hemolysins agglutinins hemorrhaghins leukocytolysins coagulins ferments lecithin and cholesterin Basu found allergic phenomena in cases observed by him

Waterman describing the venom as found in Trinidad states that it is a transparent acid yellow liquid frothy when agitated When evaporated it leaves dark yellow scaly flakes soluble in water physiological salt solution glycerine and dilute alcohol Pure alcohol iodine, ether ammonia and tannin precipitate the venom Heating to 100 C. for 30 minutes destroys it The toxic principle is a toxalbumin containing a neurotoxin resembling that of cobra venom which acts on the medulla and motor end plates and causes death by respiratory paralysis. It also contains a lecithid which hemolyzes nucleated and non nucleated red cells as does cobra venom Waterman quotes Stitt to the effect that the mortality in young children stung by *Buthus quinquestriatus* is 50 per cent

pion caused only local symptoms but *Centruroides sculpturatus* was deadly with little local effect but with serious neurotoxic phenomena In Mexico *C suffusus* and *C noxius* have similar deadly effects Waterman states that the Durango scorpion of Mexico killed 1 608 people between 1890 and 1926 in the city of Durango (population 40 000) He mentions acute pancreatitis resulting from the venom also pancreatic cysts

According to Joyeux the effects of French scorpions are not serious and require no treatment Shulov notes the presence of 1_ species of scorpion in Palestine 5 of which are common and only one *Buthus quinquestriatus* dangerous

Hemiplegia and aphasia have been described as resulting from certain scorpion stings even in very young people Mody thinks this may be due to a clotting effect on the blood In South Africa Emdin reports depression of the central nervous system and a digitalis like action on the circulation by scorpion venom but says that death is rare even in infants

In North Africa on the contrary there are some exceedingly dangerous scorpions *Prionurus australis*, the worst of the 15 species known there being one of the most dangerous scorpions in the world An antivenin against the stings of this species protects against those of the other 14 species Etienne Sergent of the Pasteur Institute of Algeria has done notable work there in the development of this valuable form of treatment He published a series of papers on his work distinguishing between benign and grave cases in those stung In 1944 he published data on 388 grave cases 3 4 of which were cured although in 118 of them death appeared imminent In the 64 deaths he felt that the serum had been given too late in 19 in too small an amount in 15 too little and too late in 3 In 37 cases the completion of treatment was impossible Omitting these 37 and considering 3 4 cures in 351 cases he had 92 3 per cent of cures whereas death in from 2 to 24 hours was the rule without serum treatment The dose advocated in 1947 was 20 c c intramuscularly or intravenously for adults and 30 to 50 c c for children who are more susceptible to the venom and therefore require larger doses By that time Sergent had used serum in 2 _09 cases of which 531 would have been considered hopeless without serotherapy and 134 appeared actually moribund yet 47 or 88 9 per cent of the 531 grave cases were cured

ing goose flesh The mark of the sting could be seen but no swelling was there His pulse and respiration were rapid He had urgent urination vomited several times and then became semiconscious, very restless and frothed at the mouth In conscious moments he complained of severe pain throughout his body especially in his chest and the stung leg He had much cough and expectoration of fluid which soon became blood stained Then he went into severe shock and became pulseless His temperature was 96 . F, his apex heart sounds were faint their rate being 136 per minute and his respiration was much embarrassed Attempts to estimate his blood pressure showed ony an occasional beat coming through at 80 mm of Hg His whole body was in a cold sweat He developed generalized pulmonary edema with cyanotic lips, appearing moribund In his lucid moments in this period he desired to evacuate urine and feces but could not do so for an hour Then he passed a stool and somewhat later about .50 c c of urine showing 4 plus albumin a specific gravity of 1 018 no sugar, a moderate number of hyaline and finely granular casts occasional red cells and many leukocytes After 2 more hours he had improved so much that he was taken home from the hospital but for 2 days had generalized pains maximal in his chest The scorpion was described as small about 5 cm long but rather darker than the usual small type

The 10th edition of Manson-Bahr s book on Tropical Diseases has the following Scorpions are very common in the tropics and their stings are not exactly dangerous except to young children, in whom, in addition to local symptoms muscular cramp profuse perspiration pyrexia vomiting and convulsions may be produced Deaths have been reported from North and South Africa the West Indies, Mexico, Korea and Manchuria ' Basu notes that Manson Bahr reports no deaths from India but that his experience differs on this point for from 1928 to 1937 19 patients with scorpion stings were admitted to the Calcutta Medical College Hospitals ranging from 2 to 32 years of age of whom 5 died all the fatal cases being in children Dey states that abortion may occur in pregnant women who are stung

There are some deadly species of scorpions in the southwestern United States and in Mexico Stahnke stated in 1938 that more lives had been lost in Arizona in the preceding 9 years from scorpion stings than from the effects of any other venomous arthropod or reptile In 6½ years there were 25 deaths from scorpions and only 10 from rattle snakes Gila monsters and other venomous animals Two species *Vejovis spinigerus* and *Hadrurus hirsutus*, the latter being the giant hairy scor

noted Sergent found that the average first dose of serum for an adult should be 20 c c intramuscularly or intravenously but a larger dose is needed in children, 30 to 50 c c being recommended in grave cases He also found that giving physiological salt solution along with the serum seemed to be of definite value using variable amounts according to the age and size of the patient often giving from 150 to 50 c c never over 500 c c was given in the reports studied His specific serum was made from horses immunized to a number of things in addition to scorpion venom It may be assumed that the standard dose will be recommended on any commercial package by the manufacturers who know the potency of their own particular preparation It should be given as promptly as possible but given in any grave case no matter how late and repeated if symptoms recur or are not relieved within a few hours If scorpion serum is not available and a snake antivenin that has proved effective against scorpion stings is that may be used

Lacking an effective serum various procedures have been recommended The use of potassium permanganate seems to have been discarded as of practically no value Great local pain may be relieved somewhat by the local injection of 1 c c of 5 per cent procaine dissolved in a 1 1 000 solution of epinephrine Many authorities recommend the application of a small amount of a strong solution of ammonia to the sting Often this seems to give prompt and adequate relief in the less serious cases and indeed is all that may be needed in the stings of the relatively harmless species When in any doubt as to possible seriousness if serum is available it should be used and there should be no doubt when any severe constitutional symptoms are present Otherwise treatment is symptomatic such as morphine for pain Basu has used calcium intravenously and when pulmonary edema occurred atropine and hypertonic glucose giving the latter in 5 to 50 per cent strength intravenously Hassan and Mohammed of Cairo found the combination of atropine and ergotoxine effective against scorpion toxin in rats and suggested its trial in man

Tombs of Bengal notes that solutions of ammonia tend to lose strength so they must be fresh when applied to the sting He recommends liq ammoniae fortis B P as stronger than ordinary household ammonia and therefore preferable and finds this effective in relieving agonizing pain In the United States the U S P aqua ammoniae fortior is the preparation of choice

Prognosis

As has been shown already, the prognosis depends on several factors the species of scorpion the age and condition of the patient, and in grave cases the availability and prompt use of a potent antivenin Far better results were obtained when the serum was given within 4 hours of the sting than when the first dose was given later than that Sergent points out that patients must be watched for several hours, when stung by dangerous species, as symptoms often recur during the first 24 hours and in such event more antivenin must be given

Prophylaxis

Dias Libanio and Lisboa secured 107 533 living or dead scorpions in 6 years for the production of antivenin paying a bounty for them This procedure significantly reduced the number of scorpions infesting that region so they advocate bounty payments as a prophylactic measure They note too that fowls seem to be resistant to scorpion stings and eat scorpions with impunity Scorpions often get into human dwellings with firewood so woodpiles should be accessible to fowls Giving a large number of chickens the run of the ground close around the house is an important preventive measure according to these authorities The main reliance, however must be on building and screening to exclude vermin in general where this can be done

Treatment

As already mentioned various specific antivenins have been produced which constitute by far the best therapy for severe cases Kraus and Rocha Botelho found that the power of a scorpion antiserum to neutralize scorpion toxin in a test tube is no index of its curative power They also found that a certain type of snake antivenin while it would neutralize scorpion toxin in a test tube had no curative action on scorpion stings They developed an effective scorpion antivenin however Wiener, on the other hand found polyvalent Lister Institute antisnake venom serum effective in neutralizing scorpion venom in the human body

Basu commenting on the need for scorpion antivenin in India mentions Todd s Egyptian scorpion serum as effective there As already

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CHAPTER XLI

ANCYLOSTOMIASIS

BY HORACE T. GARDNER

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Synonyms.—Uncinariasis, dochmiasis, miner's anemia, tunnel anemia, bricklayer's anemia, tropical or Egyptian chlorosis are common synonyms for the systemic manifestations of the disease, while for the skin lesions due to the penetration of the larvae the common synonyms are ground itch, dew itch or water itch. In Puerto Rico and the other islands of the Spanish Caribbean uncinarial dermatitis is known as mazamorra.

Definition.—Ancylostomiasis or uncinariasis refers to that parasitism

of man by one of several nematodes of the family *Ancylostomatidae* belonging to two genera, *Ancylostoma* and *Necator* In English speaking countries it is customary to differentiate between asymptomatic infection with hookworm and the syndrome of anemia caused by the worm The latter is known as hookworm disease, while the former usually is referred to as the carrier state or as hookworm infection as a contrast to the disease

History

Although a disease indistinguishable from hookworm disease was described in the Ebers Papyrus and was mentioned by Avicenna, the reliable history only goes back to 1843 when Dubini described the parasite in autopsy material obtained from a woman who had died in Milan in 1838 In 1853 Bilharz and Griesinger recognized the relationship of the worms to the syndrome known as Egyptian chlorosis It was not, however, until the famous St Gothard tunnel epidemic in 1879 80 that intensive investigation of the disease was undertaken Perroncito described the development of the ova into the rhabditiform and filariform larvae, and Grassi and Parona demonstrated that the diagnosis could be confirmed readily by the finding of the characteristic ova in the stools of suspected individuals In 1886 Leichtenstern found that, when mature filariform larvae were swallowed, they developed into adult worms, but it remained for Looss[2] to work out the life cycle of the parasite and to demonstrate that the usual mode of infection was through the skin rather than ingestion Looss had first accidentally infected himself by exposing his skin to material containing the larvae and then continued his studies on the dog hookworm *Ancylostoma caninum*

Although its presence in the United States had long been suspected Stiles[3, 4] (1902) was the first to call attention to the fact that hookworm was widely prevalent in the United States and a most important disease from a social and economic viewpoint At about the same time Ashford[5, 15] and his colleagues studied the disease in Puerto Rico Through the pioneer work of Stiles and Ashford the Rockefeller Foundation was encouraged to begin the organization of what was to become the International Health Board and the battle against hookworm was joined By its efforts against hookworm, this organization became a potent force in the control not only of the hookworm but of epidemic disease all over the world

INCIDENCE

Norman Stoll has estimated that at the present time there are probably 457 000 000 persons in the world infected with hookworm The social and economic consequences attending such a tremendous number of infections are incalculable Hookworm is present chiefly in tropical and subtropical areas and is widespread there but it is by no means absent from the temperate zones In southern Europe and other temperate climates it is more likely to be found in mines tunnels and other places where the proper conditions of humidity and temperature are available Southern Europe, northern Africa India, North China and Japan usually are given as the distribution areas of *Ancylostoma duodenale*, while in Southern India Malaya West Africa the Netherlands East Indies Polynesia, Micronesia the Southern United States and the islands of the Caribbean are the areas in which *Necator americanus* predominates However the distribution is by no means exclusive and small areas of *A duodenale* may be found in otherwise exclusive *N americanus* territory and vice versa The predominant worm in the United States is *N americanus*, but it is not unlikely that large numbers of *A duodenale* have returned from the Orient and Africa with American troops and will, undoubtedly adjust well to the new environment It is believed that *N americanus* was originally brought over from West Africa with the slave trade

ETIOLOGY

Ancylostomiasis is caused by infection with one or both of two genera of the family *Ancylostomatidae* (super family *Strongyloidea*) Of the genus Ancylostoma (ἀγκύλος hook στόμα mouth) the most important is *Ancylostoma duodenale*, the old world hookworm The other *Ancylostoma braziliense*, is responsible for creeping eruption and occurs occasionally in the intestinal phase in the tropics Two other members of this genus *Ancylostoma caninum* and *Ancylostoma malayanum* have been reported occasionally in man and the former is important from its use in the experimental study of hookworm Of the genus, *Necator*, the only one of importance is *Necator americanus*

Ancylostoma duodenale (Dubini 1843) — The adult male is about 10 mm long and about 0 4 mm wide the female slightly longer and slightly wider They are cylindrical worms gently curved antero-

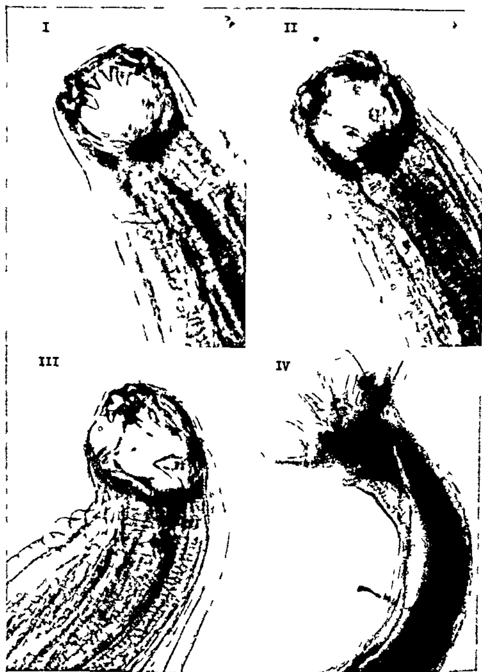


FIG 1 —Ancylostoma duodenale (From Liebow A A and Hannum C A Yale Jour of Biol and Med 1945 46 XVIII 381 with permission of the Yale Jour of Biol and Med) (I) Anterior end and buccal capsule with two pairs of teeth (II) The same but with deeper focus showing pharyngeal teeth (III) A lateral view of the same worm showing lower dental plate in addition to anterior teeth and pharyngeal teeth (IV) Shows posterior end of male with bursal rays and spicules

posteriorly and of a pearly white color The sexes are easily distinguished by the presence of the copulatory bursa in the male The posterior extremity of the female is pointed The copulatory bursa in the male is widened in a bell like manner with a tripartite dorsal ray and two pointed, non barbed spicules The mouth in both sexes is oval with four ventral claw like teeth and two small teeth of chitin dorsally (Figs 1 and 3) There is no dorsomedian tooth In the depth of the capsule there is a pair of inconspicuous teeth A single dorsal gland opens on the dorsal side of the capsule while two large ventral glands which extend half way down the body of the worm empty on the ventral side of the capsule

Necator americanus (Stiles 1902) — Necator americanus is some what smaller and thinner than *A duodenale* and has a smaller deeper mouth In place of the teeth of *Ancylostoma* it is provided with chitin ous cutting plates both ventrally and dorsally, which distinguish it from *Ancylostoma* *Necator* also has four buccal lancets and a large dorso-median tooth The dorsal ray of the male copulatory bursa in *Necator* is deeply cleft in two and the spicules are long and spiked The living adult *Necator* has a more reddish hue than does *Ancylostoma*

The ova of both *Ancylostoma* and *Necator* are similar They are thin shelled with a wide clear hyaline like area surrounding the central granular matter which consists of two or four but never more than eight segments (Fig 2)

Life Cycle of the Parasite

The ova (Fig 2) which are discharged by the female worm in the upper intestine usually in the upper jejunum are unsegmented Estimates as to the output of a single female worm per day average between 10 000 and 20 000 ova The ova are carried with the fecal material and by the time they have reached the outside world are usually in the two four or eight cell stage It is believed that the low oxygen tension in the gut hinders their development into larvae earlier However in constipated stools one sometimes sees small embryos and occasionally motile first stage larvae In undiluted formed stools further develop ment is slow and urine causes the death of the embryos very quickly If the feces are deposited in the proper soil and if proper conditions obtain the ova usually hatch within 24 to 48 hours Augustine and Smillie[1] have studied the soil in Alabama and found that the following

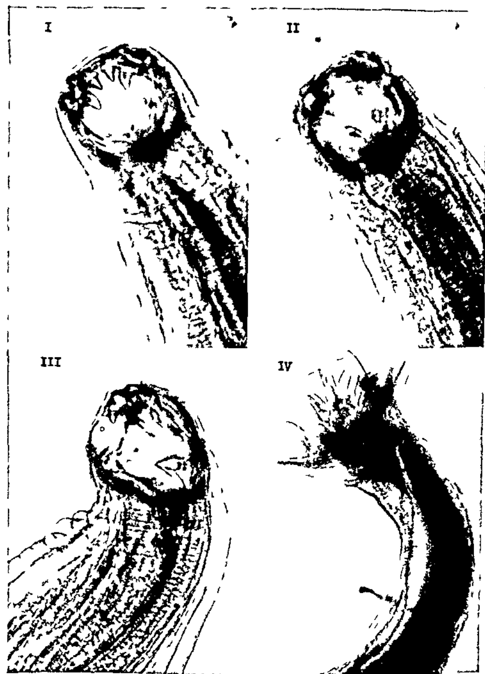


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types of soil were directly proportionate to the distribution of hookworm disease as their efficiency as culture media for the parasites was to their texture

Soil	Per Cent Development
Fine sand	39
Sandy loam	36
Fine sandy loam	2
Shale loam	9
Clay loam	5
Silty clay loam	6
Clay	3

They were unable to find larvae in polluted soil from late December until March. It has been found that the probable optimal temperature for the development of larvae is above [illegible]5 C while below 20 C is unfavorable.

When the eggs are deposited in a favorable environment with shade (and even the most primitive people tend to make their deposits in the shade) and proper conditions of humidity and temperature within 24 to 48 hours the larvae of the first stage usually have been hatched. These larvae called rhabditiform larvae are about 0.3 mm long and have a long buccal chamber a muscular esophagus and a midgut. These can be distinguished easily from the larvae of strongyloides by the very short buccal cavity and characteristic muscular esophageal structure of the latter. The first-stage larvae feed voraciously on decaying organic material in the feces or on decaying vegetation and within a short time grow rapidly. By the third day the larva sheds its cuticula and grows rapidly to 0.5 or 0.6 mm by the fifth or sixth day. About the seventh day the mouth becomes closed and the larva becomes a third stage filariform larva the infective stage for man. Cort found as a rule that the larvae do not migrate more than four inches away from their hatching place. They may retain their cuticle for some time but do not eat although they are very active and may crawl up blades of grass. After the cuticle is shed if they come in contact with the skin of man they rapidly penetrate the skin to the superficial veins of the corium. On reaching the veins they are carried passively to the lungs where they break out of the capillaries and through the alveolar walls. They then migrate and are coughed up through the bronchi and the trachea to the pharynx and are swallowed. Some time during this hegira they shed

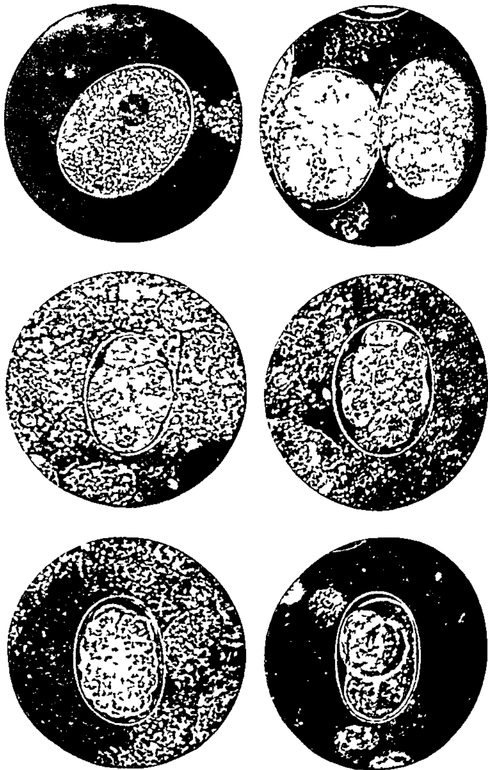


FIG —Stages of development of ovum of Necator Americanus By permission from U S Senate Document No 808 Uncinariasis in Porto Rico by Ashford and Igaravidez.

their protective cuticle and develop a mouth Then they are able to attach themselves to the intestinal mucosa (Fig 3) They may, and usually do then develop their definitive mouth and grow into adults The process probably takes about a month from penetration of the skin to sexual maturity Copulation occurs and insemination takes place by the ameboid spermatazoa of the male which the female stores in her seminal receptacles for later use since all her eggs are by no means ready for fertilization Probably a good many of the eggs which are discharged are not fertile

The period of life of the adult hookworm in man has been variously estimated as varying from a few months to seven years In the absence of re infection the vast majority probably are eliminated after a year although cases have been reported persisting as long as nine years (Chandler[8])

Pathogenesis

The disease produced by *Ancylostoma duodenale* and that produced by *Necator americanus* are essentially the same although it is considered that, other things being equal the symptoms produced by an infection with *A duodenale* are more severe than those produced by infection with *N americanus* It is also generally agreed that the incidence of uncinarial dermatitis is much less in infections due to *A duodenale* than in those due to *N americanus*

The symptoms produced by the hookworm are due to the invasion and penetration of the skin by the filariform larvae their perigrination through the circulation to the lungs and their migration out into the air sacs their subsequent attachment and development within the mucosa of the intestine and their abstraction of blood at the points of their attachment

For many years because of the lack of any considerable amount of free blood in the intestines of those persons with hookworm disease who came to necropsy and the relatively minor lesions found in the intestines many investigators felt that the anemia which is the prime symptom of hookworm disease must be due to a toxin or hemolytic ferment of some type elaborated by the parasite and this idea was supported by the fact that the worms themselves seldom were found to contain any appreciable quantity of blood

Recent investigation however has failed to substantiate the toxin theory and it is now generally agreed that although the amount of

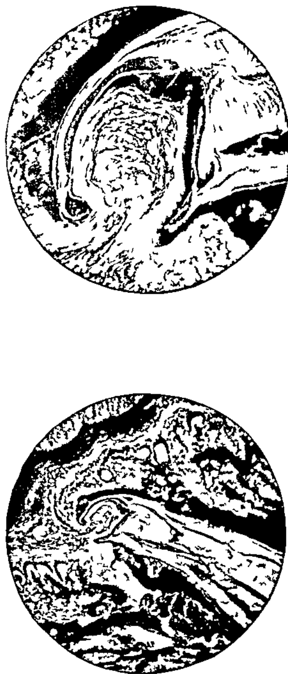


Fig 3.—Sagittal section of Necator americanus attached to the intestinal mucosa By permission from U S Senate Document No 808 Uncinariasis in Porto Rico by Ashford and Igaravidez

even in the stomach There may be evidence of a chronic gastritis with injection of the mucosa The worms may be found with their heads still attached and other areas are seen from which they have been re moved (Fig 3) These are usually small (0 5 mm) superficial ulcera tions of the mucosa which on section may reveal considerable eosino-philic infiltration about their margins These may be surrounded by a small ecchymotic halo There may be considerable amounts of ropy mucus in the bowel There is seldom any free blood in the bowel and early observers because of this and because of the fact that the worms found at autopsy rarely contain blood were led to believe in the elaboration of a toxin in the production of hookworm disease The kidneys may show cloudy swelling and there may be fatty infiltration of the liver and in the parenchymal sells of the liver there may be deposits of hematoidin

Symptomatology

It is convenient to divide hookworm infections into the symptom complex called hookworm disease and the so called carrier state Whether or not symptoms will be produced by the parasites depends upon a number of factors among which the number of worms the age of the infection the presence of superinfection or reinfection the nutritional status and resistance of the patient are all important That there is a factor of immunity as well has been adequately shown by Otto and Kerr[12] (1939) in well controlled studies on dogs infected with *A caninum*

Smillie and Augustine[11] have suggested a grouping of those infected by using the word carrier for those whose worm load is below 100 *using the Stoll technic and hookworm disease for those with worm* loads above this Although Stiles objected to this on the ground that it did not take into consideration those individuals who displayed no objec tive signs of hookworm disease but who had subjective symptoms it is very useful in the classification and treatment of large numbers They concluded that a worm load of greater than 500 *Necator americanus* caused marked retardation of normal growth and development in height and weight and lowered the hemoglobin of children of school age and that 100 to 500 caused measurable effects of the disease

Hookworm disease *itself may be divided into mild* moderate and severe grades *Mild hookworm disease* is characterized by slight or

blood may be small as taken by each individual worm (roughly estimated by Faust to be about 0.67 c c), the chronic loss of small amounts from intake by many hundreds of worms together with oozing of blood from abandoned sites of attachment is sufficient to produce the anemia

Confirmation of the probable lack of any particular hemolytic toxin in the disease was shown by a different approach to the problem in the well known studies of Castle Rhodes, Payne and Lawson[9] in Puerto Rico (1934) and later those of Payne and Payne[10], who showed that patients with chronic hookworm anemia could be returned to a normal state of health with treatment of the disease with iron alone or with iron and liver extract without exhibition of anthelminthics Treatment of patients with anthelminthics alone resulted in a much slower return to normal values

Although the chronic blood loss is undoubtedly the initial cause of hookworm disease, there are many other factors which play a role Certainly the fact that most of the patients are on a deficient diet to begin with diets deficient in iron, essential vitamins and other hematopoietic substances is most important Once the disease has begun its insidious course the associated changes in the mucosa of the stomach and bowel with defective absorption are superimposed Ashford, Stiles and others called attention early to the fact that hookworm disease by its baneful effect on the population's health and energy contributed to the poverty of such a population while poverty and insufficient food stuffs paved the way for the appearance of hookworm disease A vicious cycle which is as much economic and sociological as it is medical takes place

Pathology

Except for the local changes in the bowel mucosa the findings in autopsies on patients dying from uncomplicated severe hookworm disease are those to be expected from secondary anemia The skin usually is dry yellow and waxy in appearance There may be edema of the lower extremities but there is no marked marasmus, and the subcutaneous fat still is present The heart may show hypertrophy and/or dilatation and there may be pericardial effusion The heart usually is flabby and light in color and on section shows areas of fatty degeneration The skeletal musculature usually is brownish and friable The worms may be found in the lower duodenum and upper jejunum or

themselves have escaped infection, may not notice it This may manifest itself only by laziness and shiftlessness and the return of the patient to normal sense of well being after treatment may be the first intimation to himself and others that there has been anything amiss In the more severe, moderate cases there may be in addition to the foregoing epigastric distress and tenderness a sallow appearance and complaints of weakness and easy fatiguability There may be hypotension tinnitus aurium and dyspnea The hemoglobin may be low 60 to 70 per cent without any great decrease in the number of erythrocytes In most cases there is a moderate eosinophilia This stage may remain as such for many years but often with reinfection or with a lowering of the dietary intake the moderate picture may merge gradually into the severe picture In the United States the most frequent picture seen is the preceding but occasional severe cases are seen

The severe picture is one of profound anemia and the patient presents a distressing sight The lips and nailbeds are pale the face is dull in expression (Fig 4) the features when not edematous are sharp and drawn the alae nasae flaring with respiration as in pneumonia The skin is dry and pale yellow-gray in color The hair is scanty and there may be edema of the extremities or even generalized anasarca (Fig 5) Usually there is marked palpitation of the heart with pulsation of the neck veins accompanied by dyspnea The abdominal appearance may be that of the pot belly and there usually is marked epigastric tenderness The liver may be palpable The red blood cell count may be between 2 and 3 million per c c or as low as 900 000 The color index usually is below one except in some cases when it may simulate pernicious anemia There may be a moderate leukocytosis early but usually the leukocyte count is within normal limits

Skin

Ashford King and Gutierrez found that 90 to 95 per cent of their patients in Puerto Rico gave a history of ground itch or mazamorra, as it is called there and it is true that one usually can obtain a history of an attack of ground itch dew itch or dirt itch in most patients suffering from hookworm disease in our own Southern States On the other hand in Egypt and in India where ancylostomiasis due to *A duodenale* is very common a history of ground itch is not obtained so commonly

negligible lowering of the hemoglobin content of the blood together with vague subjective symptoms including a loss of energy vague feelings of depression and fatigue and the finding of the ova in the stools *Moderate disease* shows moderate anemia, epigastric distress and tenderness some dyspnea on exertion, cardiac palpitation and of course, loss of energy In *severe hookworm disease* the hemoglobin may fall as low as 1 gram per 100 c c , and ranges of 5 to 8 grams per 100 c c are not uncommon The red cells may fall to below one million per c c The patient in this grade of disease shows all the effects characteristic of a chronic hypochromic anemia together with the signs of severe malnutrition, hypoproteinemia and usually, avitaminoses

Acute Form of Hookworm Disease

In soldiers exposed to a single massive infection in Assam and Burma during the recent war Rogers and Dammin[13] called attention to the early gastrointestinal symptoms which occurred shortly after exposure in their series These differed from the classical both in their severity and in the abrupt acute and disabling nausea abdominal pain and diarrhea which were prominent

As a rule within about 60 days after a heavy exposure a fairly rapid onset of symptoms with rapid development of anemia defines the acute disease There may be sudden pains in the stomach, marked epigastric tenderness a sudden loss of strength and increase of pallor with a very marked and rapid drop in hemoglobin and total red cell count This type of disease is not seen frequently except in fairly overwhelming infections Ashford says that it was seen in Puerto Rico usually in persons with chronic hookworm disease who had a heavy superinfection during the rainy season and remarks that it is not usually seen in healthy persons but rather in those whose nutritional status is already precarious

Chronic Hookworm Disease

The onset usually is insidius with the patient unable to put a definite date on the appearance of symptoms In the light cases there may be no apparent anemia on physical inspection, and the symptoms may be vague There may be gradually progressive, mental dullness and retardation of so gradual a nature that the immediate family, should they

themselves have escaped infection, may not notice it This may manifest itself only by laziness and shiftlessness, and the return of the patient to normal sense of well being after treatment may be the first intimation to himself and others that there has been anything amiss In the more severe moderate cases there may be in addition to the foregoing epigastric distress and tenderness, a sallow appearance and complaints of weakness and easy fatiguability There may be hypotension tinnitus aurium and dyspnea The hemoglobin may be low, 60 to 70 per cent without any great decrease in the number of erythrocytes In most cases there is a moderate eosinophilia This stage may remain as such for many years, but often with reinfection or with a lowering of the dietary intake the moderate picture may merge gradually into the severe picture In *the United States the most frequent picture seen is the preceding* but occasional severe cases are seen

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The penetration of the skin by the filariform larvae occurs within a few moments of exposure to the soil containing the larvae Although it was once thought that penetration of the skin could be effected only through the hair follicles, it has been found that they can penetrate the unbroken skin The parts of the body most frequently affected by the ground itch are the feet and legs of children and of farmers who work barefoot in the fields, although any part of the body may be affected Loughlin and Stoll[16] (1947) have reported recently fomite borne an



FIG 4—Typical facial expression of the sufferers from uncinariasis By permission from U S Senate Document No 808 Uncinariasis in Porto Rico by Ashford and Igaravidez

cylostomiasis in a laundry where the infection was acquired from the handling of sheets and other linen contaminated with dejecta from patients harboring the disease They proved that such material could serve under proper conditions of humidity, etc as effective culture media for the larvae

Usually the lesions appear in the tender less cornified skin of the foot such as the interdigital webs and the inner part of the sole The first symptom is that of an intense pruritus usually noted at night on the day of exposure The affected areas become erythematous and some



Fig 5.—A typical severe case of uncinariasis A man of 5 years with hemoglobin 5 per cent red blood cells 876 000 per cubic mm white blood cells 9000 per cubic mm eosinophiles 4 , per cent By permission from U S Senate Document No 808 Uncinariasis in Porto Rico by Ashford and Igaravidez

times edematous Within thirty six hours as a rule small vesicles appear in these areas which usually are ruptured by the patient s scratching The raw bases of these vesicles exude a sticky, serous exudate which may cause the toes to become adherent particularly if there is much surrounding edema As a rule, secondary infection of the bases of the vesicles occurs and an impetiginous or pustular dermatitis follows In some patients however, the pruritus due to penetration of the larvae may be slight and transient papulation without vesiculation may be all that is noted During the period when the larvae are migrating through the circulation, transient bouts of urticaria may occur

Respiratory Tract

After being carried passively to the lungs by the venous circulation, the larvae penetrate the pulmonary capillaries, breaking through into the alveoli from whence they migrate or are carried by cough through the bronchioles into the bronchi, being coughed up the trachea to the pharynx whence they are swallowed During their passage through the lungs and the bronchi they may give rise to the symptoms and signs of an acute bronchitis or bronchiolitis Rogers and Dammin[13] (1946) in World War II studied a group of American soldiers with acute and heavy infections acquired in Assam and Burma and found that 70 per cent of their patients had a history of respiratory symptoms On the other hand in chronic hookworm disease it is difficult to obtain a clear cut history of such respiratory symptoms and they may indeed pass unnoticed A syndrome not unlike Loeffler's may well occur during this period of migration

Gastrointestinal Tract

The gastrointestinal symptoms to be discussed are not, of course, peculiar to hookworm disease and are those seen in most of the hypochromic, microcytic, iron-deficiency anemias due to chronic blood loss of whatever cause

There may be papillary atrophy of the tongue cheilosis and glossitis of varying degrees of intensity depending upon the dietary and the degree of riboflavine deficiency A rare case may exhibit the Plummer Vinson syndrome The gastrointestinal symptoms referable to the lower

tract are as insidious in their development as is the development of the anemia in chronic hookworm disease In the early mild cases the physician may ascribe them to functional gastrointestinal neuroses and indeed there may well exist such entities at the same time, if the concomitant anemia is not searched for, it may be missed on casual inspection

As the disease progresses epigastric distress and tenderness become *increasingly troublesome and in the severe cases bulemia and other perversions* of the appetite such as geophagy may be evident the dirt-eaters' of the Southern states and in certain tropical countries are examples of this it is sometimes spoken of as pica which is an old Latin word for such vagaries of the appetite The most logical explanation for this is the early hyperchlorhydria which the alkaline earths or a full stomach relieve There may be symptoms and signs of gastritis with progression of the hyperchlorhydria to a hypochlorhydria in the later stages Although occasional diarrhea may occur constipation is the rule The atony of the stomach the weakness of the abdominal wall and the constipation give rise to the pot belly which is seen in both children and adults although more marked in the former At times a sprue like syndrome may develop

Blood

The anemia may be of various grades according to the advancement of the disease but surprisingly low values of hemoglobin have been obtained in still ambulatory patients The color index usually is less than one although in occasional cases particularly in those with achlorhydria and an excessive secretion of mucus it may approach or even be greater than one

Examination of the blood smear usually reveals in the early stages an intensification of the central pallor of the individual erythrocytes As anemia progresses microcytes and a moderate number of poikilocytes make their appearance An occasional macrocyte may be seen but these are not frequent as in pernicious anemia The fragility of the blood corpuscles usually is normal In the early stages the leukocytes may be elevated but usually are not abnormal in number (Suarez[14]) and there is usually an increase in the number of eosinophiles Eosinophilia is not however always present although commonly it is to be expected The number of platelets usually is normal and there is no disturbance

of the bleeding or clotting time The average case of moderately severe hookworm disease will show from 3 000,000 to 4 000 000 red blood cells per c c, while the hemoglobin usually is below 10 grams per 100 c c Reticulocytes usually are normal or slightly reduced in number

Bone Marrow

Studies of the bone marrow usually reveal an increase in the number of normoblasts relatively as well as absolutely, and the bone marrow is hyperplastic After treatment with iron the bone marrow returns to normal There are no megaloblasts present, and the predominant cell is the small polychromatophilic normoblast contrasting with the state of the marrow in pernicious anemia, where megaloblasts are frequent

The Heart

As might be expected hypotension is the rule and palpitation and dyspnea are early symptoms Before the anemia is marked enough to cause visible changes on physical examination the patient may experience palpitation and minor arrhythmias may occur In the more advanced cases the heart is enlarged to percussion, and there is marked heaving of the precordium and pulsation of the great external veins of the neck If hypoproteinemia is present, and there is any considerable degree of edema of the ankles the appearance may suggest heart failure of the congestive type and the presence of a cardiac bruit may lend credence to the suggestion In patients with severe grades of the disease the massive edema, the pronounced tachycardia and dyspnea may suggest beri beri Indeed since most patients with such advanced disease usually are deficient in all vitamins of the B group, beri beri may exist concomitantly

Diagnosis

Although the diagnosis of hookworm disease may be made readily in tropical and sub tropical areas where hookworm infestation is heavy on clinical findings alone it is always essential to check the diagnosis with microscopic examination of the stools for the characteristic ova

However the diagnosis of mild hookworm disease may be difficult in areas where hookworm is not prevalent and this is particularly true today, when many citizens of the temperate zones where hookworm is rare have returned from war service in tropical areas

The onset may be very slow and insidious In mild cases the anemia may be moderate ranging from 8 to 11 grams of hemoglobin per 100 c c (50 to 70 per cent) and this may not be obvious on inspection of the patient A history of ground itch may not be obtained always in these patients Epigastric tenderness a slight tendency to dyspnea on exertion pallor headache and vertigo may all be present In mild infections the subjective symptoms may be predominant and because of the relatively early onset of attacks of cardiac palpitation the disease may be missed and put down to a functional basis or to a tension anxiety state The mild cases must be differentiated from the other mild hypochromic anemias

The diagnosis of the moderately severe and severe cases of hookworm disease usually is made quite readily in endemic areas and should offer little difficulty even in non endemic areas As Stiles has said The combination of anemia with underdevelopment weakness dilated heart and the history of ground itch is not likely to be confused with anything else The diseases which are most likely to simulate the appearance of severe hookworm disease and in the tropics they are frequently concomitant are malaria beri beri and heavy ascaris or strongyloides infections while in the temperate zones chronic nephritis may superficially present the clinical picture Malarial cachexia usually is differentiated by the presence of an enlarged palpable spleen and beri beri by the presence of the polyneuritis chronic nephritis by the examination of the urine and the finding of high blood pressure which is almost never elevated when the anemia is due to hookworm disease Pernicious anemia may be confused with hookworm disease at first glance but examination of the blood smear should differentiate it readily except in the rare case

Laboratory Diagnosis

The laboratory diagnosis depends upon the finding of hookworm ova in the stools but the laboratory should be used only to confirm the clinical diagnosis The presence of a few hookworm ova in the stools in a patient with a history of ground itch and an anemia with epigastric

distress does not, of course, preclude the possibility that the chief disease is carcinoma of the stomach Physicians in areas, where hookworm disease is rare are perhaps, as likely to be led astray by a laboratory finding as those in heavily infected areas

In the laboratory usually a simple microscopic examination of a film of feces will reveal the ova, and concentration methods are not necessary The ova are perhaps the most easily recognized of all the nematode eggs except those of trichuris trichiura

The ova are oval in shape and thin shelled with a strikingly clear, glassy zone surrounding a central group of granular cells usually four, sometimes two, but never more than eight in number The ova measure about 40 to 70 mu in Necator and are said to be slightly smaller in Ancylostoma For all practical purposes the eggs of both species are identical The eggs may be confused with the ova of strongyloides which they resemble closely In strongyloides, however, segmentation usually is further advanced and in the rare stools containing strongyloides eggs usually there are larvae, while in hookworm these usually are absent

In making surveys of intensity of infection and in doubtful cases, where the feces are negative to direct examination, methods for the counting of hookworm eggs and for their concentration have been devised The most important of these will be described briefly herewith

Stoll's method of dilution egg counting is widely used and is particularly valuable in the making of surveys to determine the density of infection in populations A flask or a large test tube, graduated at 56 and 60 ml is filled with N/10NaOH to the 56 ml mark, and 4 ml or 4 grams of feces is placed within Several glass beads (6 mm in diameter) are added and the contents thoroughly shaken until comminution has taken place With hard feces it may be necessary to set the tube or flask overnight in the cold when the contents are again agitated to ensure that all the eggs are free and uniformly distributed, then 1 5 ml are drawn up immediately into a capillary pipette and discharged onto a slide (2x4 inch) and covered with a 22 by 40 mm cover glass Using a mechanical stage and the low power objective of the microscope, the total number of ova in the preparation are counted and the results are multiplied by 100 to obtain the number of ova per gram of feces

Of the concentration methods the *zinc sulfate centrifugal floatation technic of Faust and his collaborators* has been recognized as one of the most effective concentration methods for general use It has the ad

vantage that not only eggs of helminths but also protozoan cysts and larvae are concentrated The steps in this technic are relatively simple The only things needed are a centrifuge centrifuge tubes and a solution of zinc sulfate with a specific gravity of 1 180 (33 per cent solution)

1 Three to four grams of the fecal material is comminuted in tap (lukewarm) water and strained through one layer of cheese cloth which has been previously wetted into a Wassermann or other small test tube

2 The tube then is centrifugalized for about a minute at about 500 r p m and the supernatant fluid is discarded A small amount of water is again added and the feces comminuted Water is again added to fill the tube and the preparation centrifugalized The process is repeated three or four times until the supernatant fluid is clear

3 When the last supernatant has been discarded a small quantity of the zinc sulfate solution of specific gravity 1 180 is added the feces comminuted as before and the tube filled to about ½ inch from the rim with the solution The tube then is again centrifugalized at 2 500 r p m for 45 seconds to a minute A loopful of the surface film then is examined under the microscope

There have been many modifications of this method but most of them are but refinements which demand special equipment Another concentration method which is widely used but which demands special centrifuge tubes and carriers with guards to keep specially ground cover slips in place is the *Lane*[19] *D C F direct centrifugal floatation method* Laughlin and Stoll[20] recently have found the *AEX (acid ether xylol) method of Telemann* as they have modified it to be an efficient con centration method for helminth ova For details of these techniques the reader is referred to the sources

Cultivation of the hookworm larvae as a diagnostic procedure by means of the Baermann apparatus is seldom necessary in practice but is useful in the testing of soil and to differentiate strongyloides larvae This simple apparatus consists of a large funnel with a rubber tube and a pinchcock mounted on a suitable stand Over the top of the funnel is placed a screen of 1 mm wire gauze which is pressed down to form a cup within the funnel A square of cheesecloth is placed on the screen the specimen of feces or earth placed on the cheesecloth and the funnel filled with lukewarm tap water so that the water just comes in contact with the soil or feces If larvae are present in the soil they can be seen migrating within 15 to 20 minutes After three days or more in a warm room the larvae which have hatched may be drawn off from the tip of

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mucous membranes of the mouth and cause painful ulcerations Two to three hours after administration a saline cathartic such as sodium sulfate is given Five hours later the patient may eat The presence of food decreases its activity The drug may be repeated after a three day interval The dose for children below six is 0 6 gm for older children 0 8 gm and for adults 1 gm The crystoids usually are prepared to contain 0 2 gm each It is wise to forbid alcohol and fats the day prior to treatment and to give a light supper the night before The patient may continue to pass adult worms in the stools for two to three weeks after treatment and it may be wise to wait that long before giving it again

Tetrachlorethylene—Tetrachlorethylene was introduced as a specific for hookworm in 1925 by Hall and Shillinger and it is probably the drug of choice if ascaris can be definitely excluded It is about 1/5 as soluble in water as carbon tetrachloride and toxicity is thereby greatly reduced provided that the intestine is free of fat There have been practically no serious toxic effects reported Lambert treated over 0 000 cases without any toxic symptoms except occasional nausea vertigo and a transient epigastric burning

Tetrachlorethylene—The dose of tetrachlorethylene is the same as for carbon tetrachloride 1 e 0 2 c c for children for each year of their age The dose for adults is 3 c c The drug is administered in the morning on an empty stomach a light meal having been given the night before It is usually administered as is hexylresorcinol in hard gelatin capsules and alcohol and fat are contraindicated the day before Two hours after administration a saline purge is given As with hexylresorcinol the worms may be eliminated for as long as a week after treatment

Thymol—Thymol has been used for many years and is still highly thought of by men with considerable experience in the treatment of hookworm Thymol is a stearoptene which is contained in the oil of *thymus vulgaris* and is methyl isopropyl phenol As it is considerably more toxic than the drugs which have been mentioned it should be used with caution in the aged the infirm and those with very severe grades of anemia It should not be given if gastritis dysentery or nephritis are present and is contraindicated in cardiac disease The toxic symptoms result from its stimulating action on the central nervous system and tinnitus euphoria confusion and delirium may supervene followed by coma and death Of the milder symptoms tinnitus and headache are most frequent The drug is given in a dose of 4 gm for an adult 0 5 gm for children below the age of five and 0 95 gm in children

the funnel It is necessary to obtain expert parasitological opinion to differentiate adequately between the larvae of strongyloides and some of the free living nematodes when earth is being examined

The differentiation between *Ancylostoma duodenale* and *Necator americanus* sometimes can be made by obtaining stools after a purge and finding the adult worms

Treatment

The treatment of hookworm disease is rationally directed first against the parasite and then against the anemia which has resulted but in very sick persons in whom the anemia is severe, it may be necessary to proceed in the treatment of the anemia before administering a vermifuge

Vermifuges

The drugs used most extensively in the treatment of the infection as vermifuges today are hexylresorcinol (1 3 dihydroxy-4 hexylbenzol) and tetrachlorethylene ($C\ Cl_4$), they have the advantage of a relatively high margin of safety and therapeutic efficiency

Hexylresorcinol—Hexylresorcinol is of particular use in the treatment of hookworm because it is also effective against ascaris, and its use obviates the dangers inherent in the use of carbon testrachloride thymol and tetrachlorethylene in cases where a concomitant masked ascariasis may exist Its value as an anthelminthic is not as high since at the first administration it will remove only about 75 per cent of the hookworms but it will remove 95 per cent of roundworms such as ascaris A combination of use of the hexylresorcinol initially followed by one of the other more potent drugs is being used increasingly with success Carbon tetrachloride and thymol as well as tetrachlorethylene cause irritation to the ascaris and they may begin to migrate with sometimes unfortunate results Perforation of the intestine, invasion of the extrahepatic biliary system and other bizarre results have followed the administration of one of these drugs Hexylresorcinol is non toxic The drug is given in hard gelatin capsules in the morning on an empty stomach Care must be taken in administering the drug to children to see that the capsules are not bitten as the drug can be irritating to the

against both ascaris and hookworm but is also effective against the renal and hepatic cells It should no longer be used in the treatment of hookworm It is especially dangerous in children Smillie reported only 22 deaths in over a million persons treated with the drug yet he believes as an ascaricide hexylresorcinol is to be preferred The usual dose of 1 5 to 3 c c in three parts at hourly intervals should be given to the patient without any preparation except a high carbohydrate diet for a few days before He should not be purged nor should he be fasting The dose is given in hard gelatine capsules An ounce of magnesium sulfate should be given one hour after the last dose The symptoms of toxicity are nausea vomiting and tinnitus These may be followed by convulsions Hematuria and jaundice also have been observed The treatment is to give a saline cathartic to eliminate the drug and administer fluids to protect the kidney from high concentration of the drug

Anti anemic Therapy

As already intimated treatment of the anemia is a very important factor in the treatment of hookworm When anemia is severe its treatment actually is more important than removing the causative hookworms When anemia is very severe its successful therapy should antedate the giving of a vermifuge the latter given too early may even cause death For the anemia iron should be given promptly and in large doses The use of ferrous sulfate (exsiccated) in capsules 1 gm daily or ferric ammonium citrate 6 gm in a 50 per cent solution daily Children should receive proportionately smaller doses of iron in proportion to their weight It is suggested that smaller doses of iron than those just mentioned should be given for the first few days

When the patient is markedly anemic prompt blood transfusions should inaugurate the accompanying iron therapy

A liberal well balanced diet should be given and increased to high caloric value as rapidly as lack of appetite and nausea are overcome

Prognosis

With adequate iron intake attention to the general nutrition and proper treatment with anthelminthics the general outlook for hookworm

from 5 to 10 The patient should be given a saline cathartic the night before and the drug should be given in divided doses Lane recommends that the whole dose be divided in three parts and taken at intervals of one to two hours Women should receive a slightly lower dose (3 gm) and if pregnant, the dose should only be 1 gm The drug should not be given at more frequent intervals than a week If toxic symptoms should supervene the treatment should be directed toward the removal of the drug as in phenol poisoning with such supportive measures as are indicated

Carbon Tetrachloride—This drug has a very high efficiency against hookworm but it is also very toxic to the liver It is not an ascaricide and for that reason should not be given unless ascaris has been eliminated or unless one gives it together with an ascaricide such as oil of chenopodium Smillie (1939) and others have reported deaths following its use It is contraindicated in the presence of cirrhosis liver damage of any kind in hypocalcaemic states in alcoholism and in the presence of respiratory infections The dose, after preparation by abstinence from alcohol for several days together, if possible with a high carbohydrate high protein high calcium diet, should be given in the same manner as tetrachlorethylene Since it is used mainly in the mass treatment of the disease because of its cheapness it is not always possible to have adequate preparation of the patient and for this reason those using the drug *should be on the alert for signs and symptoms of toxicity*

The symptoms of acute poisoning from carbon tetrachloride are referable to the central nervous system Increased neuromuscular irritability, confusion hallucinations and disorientation may be present, and the patient might be taken for an inebriate If the patient survives the acute symptoms of poisoning and even if they have not been evident the symptoms and signs of chronic poisoning may come on after 48 hours Nausea, vomiting and the development of the signs and symptoms of an acute hepatitis may supervene The patient may die from acute central necrosis of the liver The treatment should consist of prompt administration of glucose parenterally if necessary a high carbohydrate, high protein, high calcium diet In addition to the liver the kidney usually is affected with cloudy swelling and extensive tubular damage

Beta napthol—This drug has long outlived its usefulness and should no longer be used in the treatment of hookworm disease It is extremely toxic to both liver and kidney

Oil of Chenopodium—Oil of chenopodium is obtained from the Jerusalem oak and the active principle is ascaridol which is effective

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disease is very favorable The disease is much more serious in children than in adults and in the lighter skinned races than in negroes and orientals Because of the nutritional deficiency and the anemia patients are much more likely to succumb to intercurrent infections than to the hookworm disease itself It is difficult to arrive at an accurate figure in regard to mortality, since there are so many other factors to be considered Estimates have varied from ½ to 7 per cent mortality In pregnancy particularly if the pregnancy is advanced, severe hookworm disease carries a grave prognosis

Prevention

The International Board of the Rockefeller Foundation introduced the intensive method of control in 1909, a combination of sanitary measures to prevent soil pollution and treatment of infected persons This campaign against hookworm probably was one of the most extensive campaigns against any disease ever undertaken, and the results have more than justified the work not only in the decrease of hookworm but in the general lifting of the sanitary standards of the communities in the south By working through the organized health organizations this great fight against hookworm has accomplished far more than its immediate goal in establishing the confidence of the people in their public health departments

The problem of control of hookworm disease is by no means simple and is almost inextricably interwoven with social and economic problems of the first magnitude, but that it can be solved as been shown by the results of the work of Ashford, King and Gutierrez in Puerto Rico and of Stiles and the Rockefeller Foundation in the southern United States Keller, Leathers and Densen [1] have found a -/3 decrease in incidence of the disease between the years 1910-14 and 1938

It is obvious that the prevention of the disease depends upon the control of soil pollution with feces from infected individuals Education of the people in endemic areas to the dangers of soil pollution and of the need for properly constructed latrines combined with treatment of infected individuals are the tried and valid tools in the control of the disease Justin Andrews [2, 23] in recent reviews has pointed out that the family rather than the individual is the unit of control He has emphasized also the detection, prevention and control of hookworm disease rather than the elimination of hookworm infection The education of the individual

and, more pertinently the family in the use of a sanitary privy or bored hole latrine can be brought about by a teaching of the simple life cycle of the parasite That this can be done even among the poor and ignorant was shown by Ashford and Gutierrez in Puerto Rico Stoll has pointed out that however efficient a deep pit latrine or a sanitary privy may be that its efficacy is proportional only to the extent that it is used and says What we need is to find a convenience of civilization, an excusado as attractive in its way as is the filling station comfort room

Undoubtedly hookworm will tend to disappear as the general level of education and public health improve and improvement of economic health among the depressed classes will be followed by the wearing of shoes except in the tropics and by better nutrition and consequently less hookworm disease

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CHAPTER XLI-A

TRICHINIASIS

By O H PERRY PEPPER

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Definition — Trichiniasis (or trichinosis) is a disease caused by a minute nematode worm *Trichinella spiralis* transmitted to man by the ingestion of infected hog meat and characterized by symptoms of varying severity and nature in the several stages of ingestion dissemination and encystment of the larvæ

Historical

For many years before the disease trichiniasis was recognized the calcified cysts had been seen in human muscle (Tiedemann 1822 Hilton 183) To Sir James Paget[1] however usually is given the credit of being the first to recognize their true nature while working in the dissecting room as a first year medical student in 1835 In the same year from material from the same cadaver Richard

TABLE I

TRICHINELLA SPIRALIS IN RELATION TO TRICHINIASIS

Period after Ingestion	Approximate Length in mm			Life History	Demonstrable best in	Chief Symptoms	Eosinophilia
	M	F	Larva				
1st Day	1.2	1.5	—	Larvae reach intestine and escape from cysts	Feces	Diarrhea	
2nd Day	1.5	2	—	Mature and copulate	Feces.	Diarrhea	
6th to 10th Day	1.5	3.4	0.1 ↓ 0.5	Larvae born Larvae enroute to muscles.	Blood Spinal fluid.	Facial edema Serous surface irritation Onset of myositis	Appears
10th to 21st Day			0.9 to 1	Most larvae reach muscle	Muscle	Height of myositis	Highest
3rd to 6th Week				Larvae become encysted Adults die	Muscle	Emaciation Most of deaths	
Later	Cysts 0.4 by 0.25			Calcification of cysts	Muscle	"Trichinal rheumatism"	Slowly disappears

Owen described and named the parasite The next link in the chain was supplied by Leidy who in 1847, discovered the encysted larvæ in the muscle of the hog

It was not however until 1860 that the final step was taken A young girl in a hospital in Dresden was thought to have typhoid fever, but there was an unusual symptom severe muscle pain When death ensued and no ulceration of Peyer s patches was discovered at autopsy, Zenker, remembering the pain, examined the muscles and found many trich næ He also discovered adult worms in the intestinal tract and was able to trace the source of the infection Zenker learned that some of the offending meat had not been so'd by the butcher because of the illness of a number of his customers, and he was able to demonstrate trichinal cysts in this meat This established the identity of the disease and soon afterwards Virchow and Leuckart succeeded in tracing the life history of the parasite

Further steps in the history of the disease include the important discovery of the associated eosinophilia by Thomas R Brown[2] in 1897 and the demonstration of the larvæ in the circulating blood by Herrick and Janeway[3] in 1909 and in the spinal fluid by Van Cott and Lintz[4] in 1914

Still more recently has come a proper appreciation of the high incidence of this infection in the hog and in many other animals including rats, dogs and bears, and the frequency of the disease in man

Significant items are lacking for a history of the prevention or treatment of the disease *For many years confidence was placed in prevention* by meat inspection Little by little this proved impracticable and inefficient, today it has been largely abandoned and the responsibility for prevention has been placed wholly on proper preparation of the meat

Etiology

A full description of the etiologic agent, *Trichinella spiralis*, will be found in Chapter XXXVIII of Volume V and this need not be repeated here Table I outlines the life cycle and growth of the parasite and the relation of the various stages to certain clinical features of the disease and will help to a more intelligent understanding of the disease as seen in man

It is important to appreciate the enormous numbers of worms involved in an average infection A single ounce of heavily infected pork may contain as many as 50,000 encysted larvæ, if one half of these are viable females and each produces the usual 1 000 or 1,500 young it can easily be seen what a heavy 'dose' of infection may occur after a heavy meal of inadequately cooked pork inflected to this degree

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10th to 21st Day			0.9 to 1	More larvae reach muscle	Muscle	*Height of myositis*	*Highest*
3rd to 6th Week				Larvae become encysted Adults die	Muscle	Late edema Most of deaths	
Later	Cysts 0.4 by 0.25			Calcification of cysts	Muscle.	Trichinal rheumatism	Slowly disappears

TRICHINIASIS

Epidemiology

Although trichinella are found in a great variety of carnivorous animals, it is the infection of the rat and hog which bears directly on the infection of man It is the rat which exhibits the highest incidence of trichiniasis and probably is sufficient alone to perpetuate the infection through its cannibalistic habits" (Stiles) The hog is infected by the eating of infected rats or their dejecta, uncooked infected pork in garbage or swine offal Man with his existing dietary habits usually is infected only by pork, but under altered conditions might obtain the parasite from any of the other infected animals such as foxes or bears In some districts almost 100 per cent of rats are found infected while figures for hogs have seldom exceeded 6 per cent Fishes, crabs and lobsters are not known to harbor the parasites, and it seems doubtful if infection from fowls ever occurs Augustine has shown that in birds many ingested larvae are destroyed in the gizzard and that most of those which successfully pass the gizzard are promptly destroyed during dissemination in the body Neither the adult worm nor the larva can withstand gastric digestion, but in man the encysted larva is not freed from the protecting envelop until past this danger

Trichiniasis in man then is almost solely dependent upon the ingestion of infected and inadequately cooked pork, although cases due to the eating of infected bear meat have been reported from California and Germany[6, 8] The disease may appear in small epidemics spreading from a single butcher a single hog or inadequate cooking at a hotel or picnic It is common in neighborhoods supplied from country slaughter houses where rats abound Greater frequency is noted in those countries, especially North Germany where raw ham and sausage are eaten In the United States the growing popularity of sausage and roadside barbecue[9] makes one fear an increase in the disease In 1941[10] in an examination of 3 000 diaphragms from cities in the eastern United States 488 or 16 per cent were found infected Wright[11] similarly found 17 per cent but only 0 7 per cent among Jewish persons undoubtedly due to the rules of their religion

In this country the disease is more common among Germans and Italians but no one is immune Children often seem to escape, but perhaps their portion of meat is more sure to be well cooked or their diarrheal reaction sufficient to rid the body of the majority of the parasites There is no seasonal influence except that it is in winter that the eating of uncooked pork products seems to be most frequent

The factors in prevention will be discussed later, but it is important to emphasize that in this country there is no state or federal inspection of pork for the presence of trichinae

PATHOLOGY

No characteristic changes are recognized as accompanying the gastroenteritis which may follow promptly upon the ingestion of infected pork Indeed it is not known whether the fever diarrhœa and vomiting which occur in some



FIG 1 — Trichinal cyst from human pecto al muscle Note the surrounding myositis and the polar cells Courtesy of Prof Balduin Lucke

instances but not in others are due to the presence of the parasites in the pork. Some (Karsner for example) assume a toxic irritant released by the digestion of the cyst wall others attribute the gastroenteritis to a non specific cause (ptomain) pointing out that pork which will lead to trichiniasis is very apt to be spoiled and must have been inadequately cooked

The true pathology of trichiniasis commences with the birth of the new generation of larvæ and their dissemination throughout the body It is in the voluntary muscles that the pathology is best known and most constant, but the larvæ enter the various serous spaces where no doubt some degree of reaction is set up This latter is best seen in the meninges and even in the brain itself

Myositis is the term commonly applied to the widespread changes in the skeletal muscles, the process, however, is scarcely a true inflammation The larvæ penetrate individual muscle fibers which degenerate about the parasite Similar degeneration may be seen in adjoining fibers but to a less degree. Within the muscle fiber the larva continues to grow until after about two weeks it has increased its initial length tenfold and has assumed a coiled position The worm now lies in a space within the degenerated muscle fiber which will become the so called cyst There is uncertainty as to the formation of the wall of the cyst, the theory originally advanced by Loeschcke that the cyst capsule is a precipitate formed by the organism of the host is not generally accepted Others derive the cyst wall from intermuscular connective tissue, and it is true that within the final cyst one can often see remnants of the nucleus and striations of the invaded muscle fiber

Within a month after infection the cysts have appeared, but they are not fully formed until a month later About this time groups of large cells appear at the poles of the cyst (see Fig 1), these have usually been termed "fat cells," but more recent opinion[11] considers them to be macrophages of reticulo-endothelial origin Calcification of the wall is believed to commence after about six months and to be complete after about a year

Eosinophilia in and about the lesions in the muscles is not a constant finding but occasionally may be quite marked It was first noted by Brown who searched for it after finding the circulating eosinophilia An interesting observation was made by Howard[12] that in a patient who had no circulating eosinophilia many eosinophiles were present in the muscles

The calcified cyst usually of lemon shape in both man and hog (spherical in rats) has an average length of 0 4 mm and to the unaided eye appears as a minute opaque or greyish point in the muscle In human muscle the calcification is readily felt but unfortunately this is less evident in pork and may even be totally absent Under the lens the coiled worm can be seen readily, occasionally there are two or three within the cyst After some years the larva may die degenerate and perhaps become calcified

The muscles most heavily invaded are those in most constant use and with the freest blood supply the diaphragm (see Fig 2) and intercostals, the tongue, the masseters and the muscles of the eye and larynx This distribution is of importance in explaining some of the common symptoms of the disease Of the

peripheral muscles the gastrocnemius and deltoid have at least a clinical repu tation as sites of heavy invasion Trichinal cysts have been found by Broders in the muscle tissue removed with the tonsil in twelve of 10 000 tonsillectomies

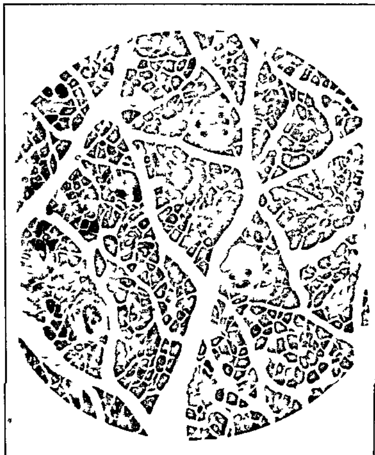


Fig 2 — Recent trichinal cysts in human diaphragm Section unstained Courtesy of Prof Baldwin Lucké

Larvæ during the stage of dissemination are widely spread by the blood stream throughout the body They have been demonstrated in many organs including the brain lungs liver pancreas and heart They also appear in various serous spaces including the peritoneum and pleura, and in the subarachnoid space In the organs just mentioned the larvæ may escape from a capillary and cause local destruction of tissue Except in the brain and lungs such

lesions apparently are of little importance In the brain there may occur a gliosal reaction as well as a distinct meningeal irritation with increase of cerebrospinal fluid and its cellular content[13, 14] The lesions in the lungs may be sufficient to cause respiratory symptoms and may be analogous to the picture seen in the pulmonary manifestations of ascaris infection The hematological changes will be discussed later

An excellent review of the pathology of trichiniasis with extensive references to the literature has recently appeared[1]

Symptomatology

It is of primary importance to appreciate the great variability in the severity of the clinical features of trichiniasis In any epidemic there will be cases so mild that only by the finding of an eosinophilia is one led to a confirmatory biopsy and other cases of great severity and duration Also, the symptomatology will differ widely in cases from the same source one may have no diarrhœa but severe myositis another the reverse There is, however, a symptom picture to which many cases conform and in which the symptoms clearly correspond to the stages in the life cycle of the parasite

Stage of Immediate Gastroenteritis

Soon after the ingestion of the infected pork there may appear fever, nausea, vomiting diarrhœa and abdominal cramps As has been said above it is not known whether these symptoms are due to the products of the dissolving cysts, or to the fact that the meat itself may be spoiled or uncooked These symptoms may be wholly absent, very mild or so severe that death may occur at this stage

The later course of the disease bears no relation to the severity of these onset symptoms unless it be that prompt purging rids the body of many of the parasites This has been advanced as an explanation for the mildness of trichiniasis in children in whom severe gastroenteritic manifestations are apt to be present In some cases the fever appearing at this stage persists, and the patient continues ill into the period of invasion, others return promptly to health and may forget the trifling digestive upset

Stage of Invasion

On the sixth day or a little later appear the symptoms resulting from the arrival in the tissues of the newly born larvæ Fever between 101° and 105° F usually is present at this stage, but Conner[16] has pointed out that even the

fever may be absent The patient experiences headache and malaise and sometimes there occurs a return of diarrhœa

The muscles become painful sore and swollen According to the areas chiefly involved the clinical picture may differ enormously In the usual case the chief discomfort involves the muscles of the extremities and the arms and legs may be considerably swollen The invaded muscles are tender to the touch and give a sense of increased resistance suggesting India rubber Sometimes pain will be absent but on pressure one may elicit tenderness especially near the ends of the muscles On the other hand pain may be so extreme that function is almost abolished suggesting a true paralysis There may be a cautious almost characteristic gait Invasion of the extraocular muscles results in pain upon movement of the eye the masseters are commonly invaded and chewing becomes difficult Tenderness of the neck muscles leads to stiffness of the neck and pain upon movement of the head Intercostal and diaphragmatic myositis cause pleurisy like pain with each respiratory act The tenderness and pain of the abdominal muscles may be such as to simulate some acute intra abdominal process Phonation and deglutition may become painful and difficult

Edema usually is present early in this stage Sometimes it is limited to the limbs but as a rule the face and especially the eyelids are markedly swollen This has given rise to the term frog face of trichiniasis Usually the skin over the edematous areas is not reddened but occasionally there occurs sufficient erythema to suggest an inflammatory origin for the swelling Herpes labialis is common pruritus may be present and the appearance of rose spots resembling those of typhoid fever has been reported

An excellent description of a case in this stage is to be found in the following note written on December 2 1897 by Sir William Osler on a case of trichiniasis in the Johns Hopkins Hospital which case was reported in the literature by Dr William S Thayer[17] under the title A Third Case of Trichinosis with Remarkable Increase in the Eosinophilic Cells

The face and eyelids are puffy the face suffused and red the tongue clean the arms and hands much suffused the latter being cyanotic they are closed with difficulty as they are so stiff The feet and arms are considerably swollen particularly over the backs and wrists where they are puffy The swelling of the arms is actually in the muscles which are sore there is distinct soreness over the biceps no distinct soreness exists over the muscles of the trunk The feet are livid the legs still and cold the muscles of the calves are not particularly swollen not very tender

Ocular manifestations may be so pronounced as to lead the patient first to an ophthalmologist The swollen eyelids and the pain and burning of the eyes may early be the only symptom On examination the pupils are said to be dilated subconjunctival hemorrhages may be present and it is even reported

that the fundus may show hemorrhages and optic neuritis Chemosis of the bulbar conjunctiva is frequent

Respiratory difficulties may dominate the picture Many patients experience cough, and there is apt to be pain on breathing More serious is the disturbance of respiration from the limitation in function of the diaphragm and intercostal muscles Death may occur from respiratory paralysis or from pneumonic complications predisposed to by the limited expansion of the lungs

Cerebral and meningeal symptoms in some instances overshadow all others and cause great diagnostic confusion Not only can the myositis of the cervical muscles cause a rigidity and stiffness of the neck, but the muscle tenderness may result in a Kernig s sign and an associated absence of the knee jerk. Blumer states that this picture is especially common in children In addition there may occur as has been pointed out under Pathology, a true meningeal reaction and some degree of irritation of the brain itself[18] Stupor and delirium occur and the picture of meningitis even with opisthotonos is not unknown

Not all of these symptoms are apt to be present in any one patient but any combination may be seen As a rule, within a few days the edema disappears, the symptoms from serous surface irritation lessen and the picture becomes one of fever and myositis The fever may fall by lysis within a week or two or may continue at a high level for several months On an average, the fever in a severe but not fatal case will end in about six weeks In those instances with marked pyrexia the usual results appear, the tongue is dry, the body wasted, anorexia and headache are complained of, and sweating may be profuse

It is between the 10th and the 21st days after ingestion that the muscular pains are at their height but they may persist for a much longer period and in fact may merge in a more or less chronic state sometimes called trichinal rheumatism which may last for years Again it is worth mentioning that the muscle pain may at times be trifling and fle ting

Late Stage

In the fourth week certain new features enter the picture About 90 per cent of cases at this time experience a return of edema The late edema also chiefly affects the face and head and there is some confusion in the literature as to whether the terms ' big head and frog face' of trichiniasis refer to the early or the late swelling The late edema may rapidly come and go it may reappear several times In one patient at the Hospital of the University of Pennsylvania patches of edema appeared on the face body and limbs for almost a year At this time also pruritus may be experienced The possible allergic nature of these manifestations will be commented on in a later paragraph

By the sixth week convalescence may be well on its way, or the patient may

be in a very wasted and toxic state Late gastrointestinal disturbances may take the form of vomiting diarrhœa and hemorrhage from the bowel Death if it is to occur does so most often at about this time sometimes from exhaustion often a terminal pneumonia closes the case

Allergic Features

It seems quite likely that a number of the manifestations of trichiniasis may find their explanation on an allergic basis Urticaria pruritus the late edema and the eosinophilia might all belong in this category and it is worth noting that the late edema which may at times have the features of an angioneurotic edema appears about three weeks from the ingestion of the parasites The eosinophilia appears about the end of the first week but rises to its height in the third week

It is not necessary to assume any pre existing sensitivity for it is possible that these symptoms just as the positive skin reactions obtained with trichina extracts may be mediated by reagins and so occur in normal as well as atopic individuals[19, 20, 1]

Laboratory Features

Urinary changes are not important during the fever one would anticipate a concentrated urine with febrile albuminuria That this albuminuria is often lacking at the time of the early edema is commented on by several authorities as of diagnostic assistance An interesting report of the finding of eosinophils in the urine in a case of trichiniasis has appeared[22]

Anemia is not a feature of the disease although it may appear in protracted cases Leucocytosis and eosinophilia appear about the end of the first week and rise to their height in the third week In a general way the blood changes parallel the severity of the infection however in the epidemic reported by Aldridge[1] the two fatal cases dying late in the disease exhibited no leucocytosis or eosinophilia On an average the usual case will exhibit a total leucocyte count of about 20 000 with 20 to 40 per cent of eosinophils Far higher figures may occur the leucocytes may number over 75 000 and there are reports of eosinophilia exceeding 80 per cent

Not always is there any increase in the total leucocyte count even though a considerable eosinophilia is present On the other hand there may be a neutrophil leucocytosis with little or no eosinophil rise Long after the acute disease is ended an eosinophilia may persist even for years it is said Thrombocytosis is reported

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Intradermal reactions have been produced by Bachman[31] with the intracutaneous injection of trichinella protein in infected rabbits and guinea pigs This test is easy to perform and positive reactions appear promptly after infection

McCoy, Miller and Friedlander[3] tested some 88 persons known to have had trichiniasis within eight years and a large number of controls They state 'from a practical standpoint the trichinella skin test cannot be considered a certain diagnostic test It appears that a negative test will probably prove more useful in ruling out the diagnosis of trichiniasis than a positive one in establishing it A positive test however definitely strengthens the evidence for the diagnosis and may justify further search for the parasite Positive tests obtained with antigen dilutions of 1 10 000 or higher are of more definite diagnostic value than those obtained with lower dilutions

Before leaving the laboratory features of trichiniasis it should be mentioned that it is often possible to obtain specimens of the offending pork and examine them for trichinal cysts In doing this it should be kept in mind that the cysts in the hog are much less calcified than in the human muscle

Complications

Trichiniasis has a multitude of symptoms but few true complications Apparently the infection fails to damage the kidneys pancreas liver or spleen and only rarely the heart muscle although encysted larvæ have been reported in heart muscle pancreas kidney intestinal muscle and gall bladder[33] Pulmonary symptoms occur in perhaps half of the patients and pneumonia is a frequent terminal incident Coincident pyogenic infection phlebitis and interruption of pregnancy have been reported and latent tuberculosis is said to have been stirred into activity In general however it may be said that some die of trichiniasis but that those who recover are restored to health except in the very rare instances of trichinal rheumatism

Diagnosis

Difficulty in diagnosis is assured by the protean manifestations of the disease In many instances recognition is easy especially if more than the one individual is taken ill and it can be learned that all have eaten of the same raw or poorly cooked pork Even the isolated patient may be readily diagnosed if the classical symptom picture muscle pain edema fever and eosinophilia is present Often especially in mild attacks it is the eosinophilia which first suggests the correct diagnosis Once trichiniasis comes to mind the diagnosis can usually be proved unfortunately the disease is often not thought of probably under the mistaken impression that it is rare

Demonstration of the Parasite

In the early days of the infection the adult worms are present in the intestinal tract, but it is difficult to demonstrate them in the feces. It must be remembered that even the larger female forms reach a length of only 4 mm. and are barely visible with the unaided eye.

The blood may be examined for larvæ en route to the muscles between the 6th and 21st days. At this time, the larvæ are small and must be searched for under the microscope. Staubli[4] first recovered the larvæ from the heart blood of infected guinea pigs by laking with 3 per cent. acetic acid, centrifugalizing and examining the sediment. This is the best method available.

The spinal fluid probably will show larvæ examination only in those instances in which the symptomatology suggests meningitis. In such patients, in the second and third weeks of the disease there seems to be a good chance of demonstrating the larvæ in the specimen obtained by lumbar puncture. The fluid is clear, may contain an increased number of lymphocytes, and under the microscope the larvæ may be easily seen and recognized. Centrifugation of the specimen may help.

Examination of muscle tissue for the encysting larvæ or cysts becomes the only method of demonstrating the parasite after about the third week of the disease. It may be employed, however, as early as the end of the second week. Almost any voluntary muscle may be examined, but the biceps, deltoid and gastrocnemius for years have been the muscles of choice. Formerly the tissue was removed by one of several varieties of harpoon but surgical excision is to be preferred. The muscle tissue may be teased apart and examined under a microscope, but paraffin blocking and microscopic examination usually is necessary.

Specific Tests

The method of complement fixation has been tried for the detection of trichiniasis in hogs, and more recently Bachman and Menendez[6] found that after the twenty-fifth day after infection the antibody formation is sufficient to render the test specific. Bachman[7] also demonstrated precipitins in infected rabbits and in the serum of a man infected with trichinella spiralis. Unfortunately this Bachman test, as it is called, does not give an early diagnosis, for it cannot be used until about three or four weeks after infection. Unfortunately also it is positive with serum from individuals who have recently received quinine treatment for malaria.[8] Hunter[29] obtained positive reactions in several cases of probable but not proved trichiniasis. Bachman obtained positive results on two patients with proved trichinal infection (Stoll[9]).

forms of meningitis be excluded In the meningeal reactions of trichiniasis the spinal fluid is clear but may contain an increased number of lymphocytes and larvæ may be found Meyer[34] has reported a count of 240 lymphocytes per cubic mm in trichiniasis

Neuritis especially multiple neuritis may be simulated by the pain the absence of the knee jerks may add to the confusion Beri beri and trichiniasis may readily be mistaken one for the other for as Sir Patrick Manson[3] has written Both diseases occur in localized epidemics both may be associated with edema both are characterized by pain and tenderness in the muscles and both may kill by asphyxia arising from impaired power in the muscles of respiration

The edema of the stage of invasion leads to additional diagnostic confusion It may resemble that of a nephrosis but at this stage there is apt to be little or no albuminuria, and the other evidences of nephrosis are lacking Rarely the circumorbital edema presents an erythematous inflammatory appearance sufficient to mislead one into a suspicion of pansinusitis Sudden deafness perhaps from edema has been reported and might lead one away from the correct diagnosis

Diagnosis from Dermatomyositis — This was named pseudo trichinosis by Hepp[36] in 1887 and a review of the reported cases emphasizes the similarity of the symptom pictures of the two conditions It is true that the onset of dermatomyositis is insidious and lacks the gastroenteritis which usually but not always is present in trichiniasis and of course there will be no history of the ingestion of uncooked pork On the other hand the subsequent fever edema and the pain of myositis may be indistinguishable The edema in both may be localized at first to the face but later may extend over the limbs and body apparently it tends to be greater in dermatomyositis than in trichiniasis In the former also there is a greater tendency to some cutaneous manifestation such as erythema although urticaria is common in each The muscles involved may be the same sometimes those of the eyes sometimes those of respiration The ligneous hardening of the involved muscles must be much the same It is a curious fact that in spite of the presence of considerable fever in each condition the urine is said to lack albumin

Dermatomyositis is rare and is of unknown etiology some have suggested that it is indeed trichiniasis with destruction of larvæ in the tissues and no encystment Steiner[37] in 1905 was able to collect but 28 cases although by today[38] there are probably over a hundred recorded instances of the disease of which at least a quarter have occurred in childhood[39] Unfortunately it has sometimes been confused with trichiniasis on the one hand and with other forms of polymyositis or with scleroderma on the other Dermatomyositis has a mortality of 50 per cent or higher death resulting from respiratory paralysis or bronchopneumonia

The onset symptoms of trichiniasis may lead the patient first to the ophthalmologist, the oto-laryngologist or the surgeon rather than to the internist The symptoms may lead to a number of mistaken diagnoses of which typhoid fever, rheumatic fever, neuritis nephritis, pansinusitis, angioneurotic edema and myositis are perhaps the most important Occasionally trichiniasis may simulate an acute abdominal process, cholera or beri beri Different diagnostic pitfalls offer themselves at each stage of the disease

(a) *In stage of immediate gastroenteritis* — Unless a number of individuals are affected simultaneously or a clear history of the ingestion of uncooked pork is obtained it is very unlikely that the diagnosis of trichiniasis will be made at this stage Eosinophilia is not yet present Acute gastroenteritis, food poisoning or the onset of a dysentery will be suspected, or under special conditions, cholera In the rare instance of death at this stage some acute poisoning may be suspected

(b) *In the stage of invasion* — Pain in the extremities and fever may suggest rheumatic fever or some form of acute arthritis On examination, however, it will be found that the joints themselves are not involved but that it is the muscles and especially their tendinous ends which are tender and painful Only a careless examiner could long be deceived as to the location of the pain The gait is said to be characteristic but this must be of little practical help In appropriate districts dengue easily might be suspected at this stage

When the myositis is localized chiefly to some one part of the body, further confusion may arise Diplopia and pain on ocular movement may take the patient to the ophthalmologist and circumorbital edema also may be prominent Of three students at the University of Pennsylvania who ate infected pork the first to be taken sick reported to the Ophthalmological Department because his eyes were swollen and he felt a pulling sensation and had blurring of vision and diplopia the second had almost identical symptoms, the third also had ocular redness and swelling Tenderness and rigidity of the abdominal muscles have led to more than one fruitless laparotomy while involvement of masseters has excited suspicions of lockjaw Pleurisy may be simulated by pain arising from the invasion of the intercostal muscles and diaphragm Limitation of muscular function may be so great in certain instances, especially in children, as to simulate an actual paralysis

Myositis from other causes than trichiniasis must be considered in the differential diagnosis Suppurative myositis should give no difficulty, but the resemblance of the rare disease dermatomyositis to trichiniasis is very striking and deserves fuller consideration

Trichiniasis also may closely simulate a bacterial meningitis, delirium, headache stiff neck and a positive Kernig s sign may all be present In the absence of other evidence only by examination of the spinal fluid can the usual

deaths may occur with intense choleraic symptoms but otherwise a free diarrhœa at the onset is thought to be favorable as it leads to the ridding of the body of many of the ingested parasites before they have had time to breed a new generation Death at the height of the period of invasion most often results from respiratory paralysis while the patients who die in the late stages of the disease are apt to do so from circulatory failure or from pneumonia

In those dying from circulatory failure severe damage of the myocardium is constantly found[4] This is the more interesting in that encysted larvæ are only occasionally found in the heart muscle although the myocardial injury is perhaps due to the local action of larvæ which for some unknown reason have failed to encyst[41]

The severity of the attack and the mortality are somewhat influenced by the size of the dose of infection and by the early diarrhœa Perhaps for these reasons children tend to have mild attacks and a low mortality In epidemics due to the ingestion of heavily infected uncooked pork as for example in sausage at a picnic the mortality may reach 30 per cent but in general the mortality is nearer 5 per cent In fact if the total number of infected individuals with negligible symptoms was known the actual mortality figure would be considerably lower The figure usually given of 6 per cent refers of course only to that percentage of diagnosed cases Of Aldridge's[3] 29 cases 2 died 5 were acutely ill 17 mildly ill and 5 had practically no symptoms In another family epidemic[44] 10 of the 11 members were taken ill of whom 4 died

There is no data concerning acquired immunity in man although there is some evidence that rats do develop some immunity against subsequent infection[45]

Prevention

There are two main solutions of the problem of prevention of human trichiniasis The former places reliance on microscopic inspection of all hogs slaughtered and admits that more or less pork or pork products will be eaten raw the latter distrusts the efficacy of any inspection and insists that only when all pork is made safe by thorough cooking or other treatment will the disease disappear[4] Cooking to a temperature of 58 C is sufficient to kill the larvæ encysted in pork or refrigeration at −15 C for twenty days −18 for twenty *four hours or a rapid lowering to −35 C*[4]

In certain European countries an elaborate system of microscopic inspection of pork for trichinæ is in force but it has been pointed out that over 3 per cent of the cases of trichiniasis occurring in Germany between 1881 and 1898 were caused by pork which had been inspected microscopically and passed as free from the parasites

In this differential diagnosis the importance of the presence of eosinophilia in trichiniasis has been much emphasized[10] In dermatomyositis the white cell count is normal and there is no eosinophilia A few of the reported cases have shown some increase of eosinophils but in these the diagnosis is felt to be in doubt On the other hand eosinophilia may be lacking in certain instances of trichiniasis, especially perhaps the very severe ones Also non trichinous myositis with eosinophilia has been reported[11] Of course the final proof of the diagnosis must rest on the demonstration of the presence or absence of the trichinella the muscles in dermatomyositis exhibit marked but somewhat variable pathologic changes

(c) *At the height of the disease* — After several weeks of fever the patient may in many ways, suggest the picture seen in the fastigium of typhoid fever Even a rose spot eruption on the abdomen has been described in trichiniasis, and some writers have stressed the presence of some enlargement of the spleen While it is true that the patient may be in a "typhoid state," there is lacking all the laboratory evidence of that infection, and the presence of myositic pain and eosinophilia should be sufficient for the differentiation

Angioneurotic edema is simulated by the late edema of the fourth week rather than by that of the early period of invasion A differential diagnosis must depend more upon the course of the illness and the other symptoms than upon the edema itself or the eosinophilia These two latter phenomena exhibit no differences and indeed may arise through the same mechanism in idiopathic angioneurotic edema and in trichiniasis

(d) *In the late stage* — In protracted attacks the wasting may be extreme, and if the diagnosis has not been made earlier, a suspicion of tuberculosis may be entertained Again the pain and the eosinophilia should be of assistance as well as the absence of any evidence of localized tuberculous lesion

Finally in the post convalescent condition of persistent trichinal rheumatism, if the diagnosis has been previously overlooked confusion may arise with various chronic arthritic and rheumatic conditions Examination, however, will reveal the site of the pain in the muscles, and for some months at least the eosinophilia will still be present

PROGNOSIS

Trichiniasis may occur with little or no discomfort to the patient, or it may prove fatal In the mild attack convalescence is established within two weeks in the more severe not until a month or six weeks has elapsed Occasionally the attack is even more drawn out and invalidism for many months may result Death exceptionally occurs in the primary stage, more often in the stage of invasion and most commonly toward the sixth week of the attack Early

to be eaten uncooked trichiniasis may arise Also pork and pork products prepared on the farm are a frequent source of trichinal infection Sometimes the infection occurs during the preparation of sausage as a result of tasting the mixture to determine the need of seasoning Sometimes the disease can be traced back to the eating of smoked and dried sausage sometimes to pork which has failed to be thoroughly cooked This latter is apt to occur at picnics barbecues or under unusual conditions Of the cases seen at the Hospital of the University of Pennsylvania one group resulted from hasty cooking during house cleaning another from the lack of skill of a substitute cook

Cook pork well' is the admonition suggested and it must be remembered that the heat is slow to reach the center of a thick piece of pork this meat must be cooked throughout and not merely on the surface

Treatment

Should the condition be diagnosed in the early stage efforts should be made by purgation to rid the intestine of as many of the adult worms as possible Any active purgative will serve but calomel even up to 1 3 gm (20 grain) doses several times repeated has had a reputation for years Although some believe that the adult form dies soon after the new generation is born, yet there is evidence to the contrary and it would seem best to institute purgation at any time up to six weeks after infection

Once the period of invasion is established treatment becomes a matter of meeting such symptoms as may arise There is no known method of killing the larvae in the muscle various substances have been tried both in clinical practice and in experimental infections in animals but with no success Wright[6] for example reported in 1942 that trials with 121 chemical compounds on a large series of animals infected with trichinella failed to give any favorable results Nor does Gould[1] in his excellent monograph on Trichinosis published in 1945 mention any evidence to support the efficacy of any measures once the larvae have been disseminated through the body The literature of the past two years is equally barren

In attacks with continued fever the usual regime appropriate to any fever is of course clearly indicated Wasting and dehydration are to be combatted

Certain symptoms may demand special attention Pain in the

A trichinoscope is in common use, it consists of an apparatus by which pieces of the pork to be examined are crushed between heavy glass plates and examined with a lens and strong illumination (see Fig 3) This system is still in effect in Germany, and a good description of the method as carried out in Stuttgart is given by Kosler[48] The method is expensive and scarcely practical, it is not absolutely efficient and gives a false sense of security Also it is im



Fig 3 — Larva of Trichinella spiralis in fresh muscle Note distension of muscle fiber Courtesy of Prof Balduin Lucké

possible of application in the United States or any similar country where hogs are slaughtered on individual farms and in small community slaughter houses

It is true that in the United States this method of inspection was carried out between the years 1898 and 1906, but it was only on meat intended for export Since that date however emphasis in this country has been shifted to the destruction of the parasites by cooking or other methods including refrigeration and special curing These methods are carefully carried out in all plants operating under Federal control and the products of such establishments can be eaten in safety without cooking The pork products which are customarily eaten uncooked include certain sausages, capicola and so called Italian ham

Unfortunately, however these same products are prepared by many plants operating under little or no Federal control, and from this source of the products

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muscles may be so severe as to require morphin, sleep is often difficult to obtain even with hypnotics When the pain is limited to one area, some degree of fixation may be attempted Strapping may be resorted to in those instances in which pleurisy like pain is severe, but the tender ness of the thoracic wall may render this impossible

Failure of respiration from muscular weakness could, it seems be an indication for resort to some of the recently devised respirators, although no such case has been found in the current literature

Lumbar puncture in those instances with symptoms of meningeal irritation might have a therapeutic as well as a diagnostic usefulness

In the stage of late edema one is tempted to wonder whether adrenalin might not have a beneficial effect on the edema and the pruritus

Theoretically, one may also wonder whether encystment and calcifi cation might be hastened and perhaps trichinal rheumatism ameliorated by treatment with calcium and parathormone Again evidence is lacking

Finally in convalescence it should be emphasized that a long period of rest and good nutrition may be necessary to restore the patient to nor mal state

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CHAPTER XLI-B

ONCHOCERCIASIS

BY RICHARD P STRONG

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Definition — Onchocerciasis is the condition produced by infection with *Onchocerca volvulus* or *cæcutiens* characterized by the presence of subcutaneous fibroid nodules or tumors Secondary ocular and dermatological disturbances sometimes occur The disease is transmitted by at least five species of flies of the genus *Simulium Simulium damnosum Simulium avidum* (syn *Simulium metallicum*) *Simulium ochraceum Simulium mooseri* (syn *Simulium callidum*) and *Simulium neavei* which are indigenous to the various countries in which onchocerciasis is found to occur

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Definition. — Onchocerciasis is the condition produced by infection with *Onchocerca volvulus* or *cæcutiens* characterized by the presence of subcutaneous fibroid nodules or tumors. Secondary ocular and dermatological disturbances sometimes occur. The disease is transmitted by at least five species of flies of the genus *Simulium*: *Simulium damnosum*, *Simulium avidum* (syn. *Simulium metallicum*), *Simulium ochraceum*, *Simulium mooseri* (syn. *Simulium callidum*) and *Simulium neavei* which are indigenous to the various countries in which onchocerciasis is found to occur.

human parasites, and that hence from a morphological standpoint it is doubtful if *Onchocerca cæcutiens* is a distinct species

Geographical Distribution

The condition is common on the west African coast and has been noted particularly in Sierra Leone Liberia and southward through the Gold Coast Dahomey, northern Nigeria the Cameroons and the Congo extending eastwardly *through the Congo and into Uganda and the Anglo-Egyptian Sudan* In Africa the rate of infection varies considerably in the different endemic localities In Liberia we found it was not high but in Sierra Leone Blacklock observed that in the examination of 123 natives about 45 per cent were infected Brumpt found along the Welle River in the Congo that half the population were afflicted with tumors In other parts of the Congo Rodhain and Dubois found from 50 to 60 per cent of the adult population and from 15 to o per cent of the children attacked Hissette found in northwestern Katanga in the village of Ilebo that 73 per cent and in the village of Tangui Lonkala 61 per cent of the population was infected The writer found in some villages in the Province of Lusambo that almost every individual examined was infected

In the western hemisphere the condition occurs in the mountainous regions of Guatemala on the Pacific slope at altitudes between 2 000 to 4 500 feet and also in similar regions in southern Mexico especially in the states of Chiapas Oaxaca and Guerrero In Guatemala the writer found in a number of villages about the coffee plantations from one third to two-thirds of the inhabitants affected with onchocercal tumors In Mexico Hoffmann reported that in La Granja 100 per cent of the natives were infected and Muhlens and Hoffmann noted that in 1930–31 the infection rate rose rapidly in one district in Oaxaca from 10 to 20 per cent to 80 to 90 per cent Torre found 15 000 infected in the state of Chiapas and 5 000 in the state of Oaxaca The disease has not been observed to occur endemically in any other localities in the western hemisphere except in Guatemala and Mexico

Etiology

The adult onchocerca parasites are found in the nodules or tumors either in dilated spaces or embedded in the connective tissue of the nodules The male parasites on account of their comparatively short length often may be obtained unbroken and without great difficulty by dissection of the central portions of *the tumors However the female parasites are so interlaced within tissue that* they are very difficult to secure entire by dissection

The adult parasites are white opalescent nematodes with conspicuous trans-

History

The African condition was observed originally by a German medical missionary who found worms in the tumors of two negroes of the Gold Coast colony Leuckart, who examined this material, studied and named the parasite in 1893 *Filaria volvulus* (*Onchocerca volvulus*) Subsequently a case was reported by Labadie Lagrave and M Deguy (1899) in a native of Dahomey Prout (1901) observed two cases in Sierra Leone, and Brumpt (1904) found fifteen cases in natives in Central Africa along the Welle River Later the disease became widely known in Africa and has been studied especially by Fulleborn in the Cameroons by Rodhain in the Belgian Congo, by Dyce Sharp in Nigeria by Blacklock in Sierra Leone, by Hissette in the Belgian Congo and by the writer in Liberia and the Belgian Congo

In 1915 Robles first observed this condition in Guatemala Upon removing a tumor from the head of a child he recognized its parasitic nature In 1916, at a conference of physicians in Guatemala and in 1919, before the Societe de Pathologie Exotique Paris, he gave a detailed account of the condition and showed that it was caused by a species of *Filaria* He also emphasized that the nodules about the scalp often were associated with disturbances of the eyes and that these disappeared following removal of the tumors He also described, in connection with the disease, a definite and specific type of erysipelas, *erisipela de la costa* Subsequently Luna and Calderon confirmed these observations and reported upon the favorable results obtained by the removal of the tumors More recently the disease has been studied clinically, etiologically and pathologically in Central America by Larumbe, Hoffmann, Ochoterena, the writer and others

Brumpt in 1919 studied parasitic material sent to him by Robles consisting of one male parasite and fragments of the extremities of two females He reported that while the Guatemalan parasite was morphologically almost identical with the species of *Onchocerca volvulus* found in subcutaneous nodules in Africa it differed especially in the size and distribution of the papillæ in the male parasites and by the greater size of the spicules For this reason and also because of the data known then regarding different geographical distribution, differences in the location of the tumors in the patients in Africa and in Guatemala, as well as on account of different pathological manifestations observed in Africa and Guatemala he separated it as a new species, calling it *Onchocerca cæcutiens* or the 'blinding filaria'

Subsequent work carried out by Fulleborn (1924, 1926) and by Sandground (1933) in which a large number of parasites were studied, has shown that while there may be considerable variation in individual specimens, there are no constant morphological differences between the African and the Guatemalan

from the head and occupied 1 6 per cent The exterior pore was 34 5 per cent the cells of Rodenwaldt 63 per cent the anal pore 90 per cent and the nuclear column ended at 95 per cent Since Sandground has found no constant morphological differences between *Onchocerca volvulus* and *O cæcutiens* the latter name therefore should be regarded as a synonym

PATHOLOGY

The nodules or tumors are enclosed in a fibrous capsule and contain especially in the central portions usually several adult filarial parasites and numerous microfilariæ though the number of adult parasites in the tumor is variable In some cases the tumors are spherical in others they are lentil shaped They are found embedded in the subcutaneous tissue particularly in regions where the peripheral lymphatics converge Sometimes they lie in shallow depressions on the surface of the skull the periosteum either being adherent to or fused with the interior surface of the cyst wall In some cases the periosteum apparently has become absorbed

The appearance of the tumors studied in Guatemala and in Africa are similar The structure of the tumors varies to some extent according to their age Usually they are firm and grayish white at the periphery but there are often soft areas in the more central portions and these sometimes have a yellowish or orange color In other instances the central portions are composed of grumous material with a milky appearance It is in these soft areas or cavities that the adult parasites are particularly found together with enormous numbers of the microfilariæ

Histological examination of the nodules shows that immediately about the parasites there is often but not always evidence of an inflammatory reaction This is probably caused by the presence of the parasite A few polymorphonuclear leukocytes and endothelial phagocytes are scattered about with more numerous small round cells occasional plasma cells and eosinophils The tissue about the cut sections of the parasites sometimes consists chiefly of fibroblasts and numbers of endothelial cells lying within a more or less organized fibrinous exudate Such tissue however is not richly vascularized in the characteristic manner of granulation tissue and it has not the typical structure of a granuloma such as is encountered for example in the granulomata of either yaws or of verruga peruviana *Outside of these areas of mild inflammatory reaction* the nodule is composed largely of fibrous connective tissue In the older and larger tumors the fibroblasts may be few in number and the fibroglia fibrils not abundant the nodules in such instances being composed particularly of collagen *fibers forming wavy bundles In none of the tumors was marked evidence of* mitosis found and giant cells while often present usually are not numerous

verse annular thickenings of the cuticle and reenforced externally by spiral thickenings (bagues) This cuticular ornamentation is an essential character for the recognition of the genus, *Onchocerca* The body of the adults are filiform and tapering at both ends The head is rounded and truncated with a diameter of 0 04 mm The male measures from 18 8 to 32 mm in length, by 0 13 to 0 21 mm in greatest breadth The alimentary canal is straight and ends in a subterminal anus The tail terminates in a single spiral and is bulbous at the tip The number of papillæ is somewhat variable Two pairs of preanal and two pairs of postanal frequently are demonstrable Intermediate papillæ also may be distinguished in some specimens The two spicules are unequal, in some specimens measuring 0 082 and 17? μ respectively and may be seen protruding from the cloaca

The female is considerably longer, measuring 335 to 500 mm in length, 0 2? to 0 4 mm in greatest breadth The vulva is situated 0 4 to 0 82 mm from the anterior extremity and the tail is curved The uterus usually is filled with ova or embryos The species is viviparous

The microfilariæ, which are found present in sections of the nodules and of the dermis or conjunctiva are actively motile Great variations in size may occur Two types are apparent the smaller forms measure from 150 to 250 μ the larger forms from 285 to 360 μ in length and from 6 to 8 μ in width They possess no sheath and are not found naturally in the blood When as might rarely happen one has been seen in a preparation of the blood, it probably has escaped from a lymphatic vessel or space punctured in obtaining the specimen If a thin section of the epidermis of the face or neck or of the conjunctiva of an infected individual is made one or two up to four to eight motile microfilariæ usually are found and occasionally as many as fifty are observed

In specimens hardened in absolute alcohol and stained with Giemsa's solution two forms of microfilariæ may be sometimes distinguished In the shorter but often slightly thicker forms there is a more compact arrangement of the nuclei and they take the blue stain more readily than the larger forms Both have a thick nuclei free anterior end and a similar free posterior extremity In the small forms Blacklock (1926) found in the African parasite the cephalic clear area measured from about 5 to 8 μ and the caudal clear area from 10 to 16 μ The first break in the column of nuclei was situated at from 22 to 25 per cent of the length In the large forms the cephalic clear area measures from about 7 to 11 μ and the caudal from 13 to 18 μ The first break in the column of nuclei from the cephalic end was at from 21 to ?5 per cent of the length

Ochoterena (1930) by vital staining of the microfilariæ of the Mexican parasite found that starting from the head the non nucleated portion occupied 5 1 per cent of the total length the pre nervous region 24 2, the nervous ring ?7

After several moults have been accomplished the parasite assumes longer and more slender forms which possess marked activity and pass from the thoracic muscles particularly to the head and proboscis We have repeatedly observed all stages of the development of the parasite in the fly from the time of the ingestion of the microfilariae from the skin of the infected individual up to the fully developed infective filarial forms in the thoracic muscles head and proboscis

In Guatemala we found about 5 per cent of the wild simulium flies captured in the endemic districts infected with the parasite In one village in Lusambo Belgian Congo where the rate of human infection was very high we found 33 per cent of the wild simulium flies infected with the parasite

Only the female fly bites and transmits the infection The *Simulidæ* are day biting flies beginning to bite about 6 A M and bite freely usually between 8 A M to 5 or 6 P M The face neck feet ankles wrists and arms of natives in the endemic regions usually are exposed and the flies are frequently found *biting in all these localities*

Clinical Features

The subcutaneous fibroid nodules or tumors which characterize the disease vary in size from one to several millimeters up to some five or six centimeters in diameter The location of these nodules or tumors and their number vary greatly in different parts of the world and in different individuals

Brumpt found along the Welle River in the Congo that 99 per cent of the *tumors were located upon the body and Sharp found in Kaduma Nigeria that* in 90 per cent the tumors were found either on the chest below the axilla or *immediately above the anterior superior iliac spine on either side* In the remainder most occurred in relation to the joints simulating juxta articular nodules No tumors were seen by him on the head

Rodhain and Van den Branden in the study of 40 cases in the Belgian Congo in 1910 in no case found the tumor upon the head However in 1920 Rodhain observed one onchocercal cyst occurring on the occiput of a child The earlier observations of Bernard Ouzilleau Leiper Mouchet Dubois Clapier and others also confirm the fact that in over 95 per cent of the cases of onchocerciasis in Africa the tumor is located elsewhere than on the head

Blacklock also found in the great majority of his cases that the tumor was located upon the head However in 1927 he reported that in one village in the *Konno District 8 patients or 24 per cent of those examined had nodules on* the head Maass and Saunders also have observed a few cases in Africa with nodules upon the head

In Guatemala we found as Robles and Calderon had done that the tumor

However, Hoeppli, who studied one onchocercal tumor histologically, found numerous giant cells, and in several places the microscopical picture resembled that of a giant cell sarcoma. Martinez Baez (1935), who recently has examined 61 pieces of tumors, which originated in Africa, Guatemala and Mexico, described especially granulomatous reaction about the parasites surrounded by more or less advanced fibrous and scleroid tissue. Giant cells were numerous in many of the Guatemala tumors. He found the structure of the nodules caused by *O volvulus* and *O cæcutiens* essentially the same, though he describes minor histological differences which he believes distinguish them.

The parasite evidently is the inciting factor in the formation of the nodules. In addition to the production of the tumor about the adult parasites pathological conditions may result from the presence of the microfilariæ in the skin and in the conjunctivæ and other tissues of the eye. These changes are, in general, of a mild inflammatory nature with perivascular proliferation and infiltration of the tissues, with lymphocytes, polymorphonuclear leukocytes and plasma cells, numerous microfilariæ being present also. The eosinophils also usually are increased. The lesions in the skin and eyes will be considered in detail under the subject of Complications.

Transmission

The disease is transmitted by the bites of several species of small black flies of the genus *Simulium* and this fly is found breeding in the rather swiftly flowing streams or brooks that abound in the infected districts, the larvæ and pupæ of the flies being attached particularly to the leaves and stems of plants, especially floating grasses growing or immersed in the running water, as well as to the surfaces of stones or logs. Blacklock, working in Sierra Leone, first showed that *Simulium damnosum* is capable of transmitting the infection in Africa and described the complete development of *Onchocerca volvulus* in this fly. Shattuck, Bequaert and the writer were able to find confirmatory evidence of this fact in Liberia a short time after Blacklock's publications in 1925. In 1931 Bequaert and the writer showed that in Guatemala three species of simulium are capable of transmitting the infection in Guatemala as follows: *Simulium avidum* (syn *S metallicum*), *S ochraceum* and *S mooseri* (syn *S callidum*), while Hoffmann reported finding of developmental forms of the parasite in *Simulium mooseri* in Mexico. Finally, Hissette, Bequaert, Sandground and the writer (1934) found that *Simulium neavei* may also transmit the infection in the Province of Lusambo.

The microfilariæ, after being ingested by the fly, pass from the gut to the thoracic muscles. They first increase in length and then become very much broader, lose much of their motility and finally assume the "sausage form"

tory exudate and embedded in the fibrous connective tissue which are the first steps in the production of the nodule From the fact that the tumors often form on parts of the body where the lymphatics converge and where pressure for various reasons is likely to occur it seems possible that the frequency of the nodules on the head in Guatemala may be influenced by the lymph vessels of the subcutaneous tissues of the head becoming constricted in some way by hats or head bands worn in the daytime or by the head resting upon a hard pillow or some wooden object at night

On the other hand we are able to explain in part the great variation in the number of nodules or tumors in different districts as for example in Guate mala *and Lusambo or even in the same locality on the basis of the different* number of times that the individual has been bitten with infected flies In Guatemala where the number of nodules per infected person is not usually over 1 to 3 or 4 we never found in any district in which we worked more than 5 per cent of the simulium flies caught in the village infected with the parasite but in Lusambo Bequaert Sandground and the writer found as high as 33 3 per cent of such flies infected Cases in Lusambo with 20 to 50 onchocerca nodules were not uncommon Such individuals had been bitten probably by at least that number of infected flies probably by more However in some instances it seems extremely likely that a single fly may at one biting introduce at least several infective forms of the parasite In some villages in Lusambo practically every inhabitant was found to be infected

The tumors when situated upon the trunk usually cause little or no inconvenience When located about the joints they are more likely to cause disturbances becoming inflamed and painful When they are situated in the region of the scalp or about the shoulders ocular complications are more likely to result eventually The tumors rarely suppurate and give rise to abscess In a few exceptional instances secondary bacterial infection with abscess has resulted Such cases have been reported in Africa by Sharp Rodenwaldt and Rodhain Roubaud and Jamot incised an abscess in the subpubic region in which 10 adult male filariæ and 5 female were found entire Chesterman also has observed one case in which the parasite was present in an abscess We observed two other cases in Guatemala with abscess in which both cocci and bacilli were very numerous in the pus Ocular and skin lesions occur these are described under Complications

Infection without Nodules

While in the majority of the human cases of onchocerciasis sooner or later a definite fibrous nodule forms about the adult onchocerca as a result of the irritation which the parasite exerts in the surrounding tissues the evidence that

in the great majority of the cases was upon the scalp or in the region of the head Of the 431 cases which we studied in that country, in only 9 (2 per cent) were the nodules situated elsewhere than upon or in the region of the head While in some cases, in which small nodules may have been present upon the trunk particularly in the women, they may have escaped observation it is unquestionable that the percentage of cases with nodules elsewhere than upon the head is small

In Mexico, Hoffmann reported that the tumors were found upon the head in about 92 per cent of the cases Hence, it seems evident that in general in American onchocerciasis in the great proportion of the cases the tumor is located in the region of the head, and that in Africa in most regions usually it is found present upon the trunk or about the joints

However in 1932 Hissette found in the village of Illebo in the Belgian Congo, that in 68 cases of onchocerciasis with ocular complications 42 of these had the nodules upon the head, and in the village of Tangui Lonkala among 263 cases with tumors 97 had the nodules upon the head D'Hooghe (1935), in the Bas Uele in the study of 3 448 cases found cranial nodules in only 5 7 per cent

In number the tumors usually vary from 1 or 2 up to 5 or 6, though rarely even more nodules may be present Rodhain saw one case in Africa with 6 nodules In Guatemala it is not infrequent to find 3 or 4 and sometimes 5 or 6 nodules upon the scalp Calderon reported one case with 19 tumors

In the Province of Lusambo, Hissette Bequaert and the writer found many individuals in which there were numerous small nodules scattered over the head, shoulders and trunk, varying in number from several up to 150 or sometimes even more

We are not yet able to give a satisfactory explanation regarding the location of the tumor upon different parts of the body It has been suggested that the point at which the fly bites may be an important factor in determining the location of the tumor We have been unable to find any convincing evidence of this fact In Guatemala where the nodules occur so commonly upon the head, the flies were found very frequently biting upon the legs Also the hypothesis that the point of the fly bite determines the location of the tumor will not satisfactorily explain in Guatemala the absence of tumors on the lower extremities or trunk except in 2 per cent of the cases and the location of the tumor upon the head in 98 per cent of the cases We have no evidence demonstrating that the tumor forms in the vicinity of the point where the fly bites Most of the tumors in Guatemala are upon the scalp, which is generally covered with coarse bushy hair and most of the natives also wear hats during the daytime Nothing is known of how far or how long a period of time the infective form of the parasite travels before it becomes surrounded by the cellular inflamma

Blood

The differential count of the leukocytes usually will reveal an eosinophilia Montpellier and Lacroix have called attention to the high increase in the eosinophile cells in the blood in infection in Africa In Guatemala the writer and Bennett have found eosinophile counts varying from 25 to 50 per cent while Hoffmann (1930) in Mexico found counts varying between 20 and 75 per cent with an average of 37 per cent

Incubation Period

From the occurrence of definite nodules in young children under one year of age we have evidence that tumor formation may be completed within that period of time Robles reported the presence of a nodule in a child 2 months old and one in another child 3 months after it had entered an infected zone while Hoffmann also observed a nodule in an infant 9 months of age We have observed 6 cases in young children 4 of which were not over 10 months of age However the rate at which the nodule increases in size in all probability varies considerably in different individuals The tendency to keloid formation may be one factor in some cases In one of our patients in which a tumor of the scalp was removed the year previously a year later a new tumor measuring 1 cm in diameter was found which illustrates the size to which one of these tumors may grow in a year In two other instances the tumors had only developed to a size of several millimeters (3 and 5 mm) in a year's time Perhaps the number of adult parasites within the tumor may also influence the rate of growth of the nodule

Occurrence of Microfilariæ in the Body

The microfilariæ in the human body evidently prevail and move about freely in the center and periphery of the tumors in the corium of the skin and in the tissues of the eye especially in the conjunctiva iris and cornea They are not found in the circulating blood except by accident In general the microfilariæ are apt to be more numerous in the skin in the vicinity of the tumor than in the skin at remote places Where the tumor for example is upon the head the microfilariæ are more apt to be found in the skin of the face than in that of the legs For this reason we might expect disturbances of vision to occur more frequently in cases with tumors upon the head or neck or shoulders since the microfilariæ do not have so great a distance to travel to reach the eyes as they would in cases with tumors upon the trunk or joints The observations in Africa and Guatemala support this view We have shown that the micro-

such a tumor always occurs is not definite Certainly there are instances of human infection in which there are microfilariæ present in the skin, in which no tumor or nodule could be recognized, and in which there has been no history of a tumor (Macfie and Corson, Sharp and the writer) Hissette, however believes that in all cases of human infection a fibrous nodule is produced Whether there is not at least some fibrous growth about every adult onchocerca in man is not clear, since there have been no definite reports of the finding of adult onchocerca in man outside the fibrous nodules

Sharp alone has reported in 1927 the only instance in which a piece of an adult onchocerca (a female) was found outside a nodule In this case the dresser had removed a portion of a worm from an ulcerated condition of the foot Sharp, who examined the fragment, found it to be a part of a female *onchocerca volvulus* and from the portion of it removed numerous embryos made their escape He adds that it might have been confused with *Dracunculus medinensis*, had it not been for the microscopical findings The location of onchocerca in such a situation evidently is unusual It, however is recognized in horses and cattle that adult parasites of other species of onchocerca, *O gibsoni* morphologically identical with *O volvulus* for example, may occur free in the tissues and not enclosed within definite nodules It may be that the human species of onchocerca may also sometimes exist free in the subcutaneous tissues

Age, Sex and Race with Reference to Infection

In Africa Brumpt found the volvulus nodules three times more frequent in adults than in children and rather rare in children up to 10 to 12 years Dubois and Rodhain in parts of the Congo found from 15 to o per cent of children affected Hissette observes that in Africa few children under 3 years of age show the fibrous nodules Rodhain observed 3 cases in negroes not over 3 years of age and Rodhain and Houssiau observed a case in a European child of 5 years of age In Guatemala the cæcutiens nodules are very common in children Reference to infection in infants has been referred to The infection also is common in women but is somewhat more prevalent in men

With reference to the occurrence of *Onchocerca volvulus* nodules in the white race comparatively few reports are on record Sharp with a wide experience notes that the condition is evidently very rare in Europeans, and he himself had never seen a case Low reported one instance of infection in a white man in 1931, and Rodhain and Houssiau have noted 5 cases in Europeans, while in 1931–1935 Rodhain and Dubois Valcke and D Hooghe added 13 new cases, all of whom had lived in the Belgian Congo Protection by clothing may be a factor in this respect since in Guatemala infection with *O cæcutiens* is not very uncommon in Europeans

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Occurrence of Microfilariæ in the Body

The microfilariæ in the human body evidently prevail and move about freely in the center and periphery of the tumors, in the corium of the skin and in the tissues of the eye, especially in the conjunctiva, iris and cornea. They are not found in the circulating blood except by accident. In general the microfilariæ are apt to be more numerous in the skin in the vicinity of the tumor than in the skin at remote places. Where the tumor, for example, is upon the head the microfilariæ are more apt to be found in the skin of the face than in that of the legs. For this reason we might expect disturbances of vision to occur more frequently in cases with tumors upon the head or neck or shoulders since the microfilariæ do not have so great a distance to travel to reach the eyes as they would in cases with tumors upon the trunk or joints. The observations in Africa and Guatemala support this view. We have shown that the micro-

filariæ penetrate into all parts of the cornea, which is composed of such dense connective tissues that it is only penetrated with great difficulty by cellular elements For this reason it seems clear that the microfilariæ may also circulate freely and pass from the tumor and even through the connective tissue capsule of the tumor in order that they may reach the skin and conjunctiva It does not appear likely that the microfilariæ seek the deeper tissues of the body In sections of the skin we have not found them in the deeper layers of the subcutaneous tissue and they are not seen in the sections within blood vessels In one case of onchocercal infection in a patient 29 years of age with a tumor upon the head and loss of vision in both eyes, who died from another disease, the writer was able to secure permission to perform an incomplete autopsy The microfilariæ were found in large numbers in the periphery of the tumor, in the skin, in the corium and in the eye, especially in the cornea The examination of film preparations made from the liver and of stained sections of this organ show complete absence of microfilariæ There are no other records of any autopsies upon cases of the disease either in Guatemala or Mexico, that we know of

Macfie and Corson in three cases examined in the Gold Coast at autopsy found no evidence of microfilariæ in the viscera, though they were present in the skin Neither adult parasites nor nodules were found in any part of the body in these cases

Hissette reported that he had found onchocercal larvæ in the cerebrospinal fluid in some severe cases of infection However, d'Hooghe (1935), who has investigated this question believes that the microfilariæ do not penetrate normally into the cerebrospinal fluid and that, if one should find them after spinal puncture they probably have been derived from the skin and had passed into the needle at the time that the puncture was made

Complications

The adult parasites evidently are the inciting factor of the nodules which are formed about them The enormous number of microfilariæ circulating in the skin and tissues of the eye give rise to inflammatory changes in many individuals that possess an especial susceptibility to the products of metabolism and to the presence and movements of the parasites However, in many other individuals these secondary disturbances do not result

Lesions of the Skin

Apparently the first discovery of microfilariæ in the skin of man was made by O'Neil (1875) on the Gold Coast in the condition described as craw-craw

More recently Montpellier and Lacroix in the examination of native troops in Africa suffering with a form of itch or craw craw, constantly found microfilariæ in the dermal layer in the skin and concluded that craw craw is a dermal manifestation of onchocerciasis ('gale filarienne')

Ouzilleau Laigret and Lefrou also showed that *Onchocerca volvulus* may create inflammatory reactions of the skin which manifest themselves by pseudo-ichthyosis achromia and cutaneous atrophy

Blacklock in Sierra Leone, Macfie and Corson on the Gold Coast Sharp in Nigeria and Gibbins and Loewenthal in Uganda also found numbers of cases of onchocerciasis in which lesions of the skin were present but many other cases where the skin was normal

The writer also has found in Africa and Guatemala many cases of onchocerciasis where the epidermis is perfectly normal as far as visible lesions were concerned and in some of which numbers of the larval forms of onchocerca were present in the skin In other instances where there was slight induration of areas of the skin and slight changes in pigmentation sections of such skin in addition to the presence of numerous microfilariæ in the corium showed perivascular proliferation and infiltration of the corium with lymphocytes polymorphonuclear leukocytes and plasma cells the eosinophils being usually increased

It seems evident that in certain individuals with higher susceptibility to the products of metabolism and to the presence and movements of the parasites in the skin inflammatory changes and scratching of the skin may result In cases of long standing and severe infection with onchocerciasis in which there is severe infection of the skin with microfilariæ a xerodermatous or sclerodermatous condition of the skin may be produced

Sections of such skin in addition to the large numbers of the parasites show more or less extensive cellular infiltration in the corium In some areas the sebaceous and sweat glands are few or absent and changes in the thickness of the horny layer in the skin may occur These advanced lesions of the skin have been observed and studied recently by Fulleborn (1931) and by d Hooghe (1935) D Hooghe regards the cutaneous lesions as essentially a pruriginous affection aggravated by scratching

He further believes that the cutaneous pruriginous manifestations in onchocerciasis which may result in pachydermatous conditions lichenification scleroderma and achromia are due to allergic reactions depending upon the antigen liberated by the macrofilariæ in the sensitized human host He believes the microfilariæ in the skin play only a secondary role in the exacerbation of the allergic reactions

Shafi believes that the skin reaction produced by onchocercal infestation varies with the severity of the infection While the severity of the infection is

of importance, susceptibility of the patient apparently is a very important additional factor There is no evidence that the microfilariæ excrete a toxin Rodhain and Dubois found in skin tests made with an antigen obtained from *O volvulus*, *Loa loa* and *Ascaris*, that a much more lively reaction was obtained in patients which were subject to prurigo In one person with *O volvulus* infection and no prurigo there was no skin reaction

Erisipela de la Costa — Robles, who first described the occurrence of onchocerciasis in Guatemala in 1915 and 1910, pointed out that, in addition to the nodules upon the head and the disturbances of the eyes, the parasite produced a definite type of erysipelas which was termed *erisipela de la costa* Subsequently Luna Calderon, Azurdia and others confirmed these investigations of Robles Robles pointed out that the erisipela de la costa is a kind of myxœdema of the skin beginning with the usual appearance of acute febrile erysipelas but involving in the majority of cases only the face and head In the acute stages the whole face was swollen, the skin red, tense and shining, the temperature frequently rising to 104° F

In children particularly the conjunctivæ were inflamed, and the ears, eyelid and lips were swollen The patients complained of sharp pain in the affected skin and sometimes of sensations as if insects were crawling over the face In some cases keratitis and iritis were present

Calderon (1920) also described in detail this erysipelatous condition In the acute cases he also observed a rise of temperature but no enlargement of the lymphatic glands The tissues were swollen and discolored, and the eyes closed, partly from swelling and partly from photophobia Within 7 to 10 days after removal of the nodules all the symptoms disappeared He remarked that some of his cases were chronic from the beginning, the skin becoming gradually thickened with a formation of rugæ and of a pallid greenish tinge with œdema Exacerbation of these symptoms might occur at intervals of 1 or 2 months Eye symptoms also were commonly associated with such cases, and all of the symptoms were thought to be due to a toxin liberated by the parasites

Fulleborn in the few days that he spent in Guatemala, was unable to find any case of this acute febrile stage of the erisipela de la costa The writer also in a wide experience with the disease in Guatemala has not observed this condition as a manifestation of onchocerciasis, nor has Hoffmann met with it in Mexico Slight inflammatory reactions in the skin due to the prolonged presence of the microfilariæ have already been referred to

It would appear that these erysipelatous attacks described by Robles and Calderon were not primarily due to the onchocercal infection though in districts where onchocerciasis is so common it would not be strange if attacks of true erysipelas sometimes occurred complicating the onchocercal infection

Perhaps the term, erisipela de la costa, has been applied in the past in Guate-

mala to cases of onchocercal infection in which there has been more or less severe infection of the corium at some time with microfilariæ which has brought about a moderate inflammatory condition and in which a bacterial infection of the skin particularly with a streptococcus has been superimposed perhaps through scratching

Elephantiasis and Hydrocele

Ouzilleau Brumpt Joyeux Dubois Rodhain and Laigret in earlier years called attention to the association of elephantiasis and volvulus infection though the condition evidently is not a very common one The microfilariæ of volvulus in such cases were often found in the lymphatic glands In the regions in Africa in which such lesions were encountered other forms of filariasis occurred

Laigret reported a case in which there was a volvulus cyst upon the left side of the chest in the axillary line Upon puncture of this cyst numerous microfilariæ of *O volvulus* were obtained There was also elephantiasis of the left foot and beginning on the right foot Both legs showed greatly dilated varicose vessels There was no elephantiasis of the genital organs Upon centrifugation of the blood however microfilariæ of *A perstans* were also found, though in rather small numbers

Sharp says that the larval forms of onchocerca are often present in hydrocele fluid and confirms Ouzilleau in his association of onchocerca with cases of elephantiasis Chesterman (1935) has observed in Yakusu many cases of elephantiasis with elephantoid scrotum up to 8 and 10 pounds in weight together with large and pendulous groin glands and changes in the overlying skin D Hooghe (1935) also encountered elephantiasis and adenolymphocele in cases of onchocercal infection observed by him

Dejou (1931) has reported a case of hydrarthrosis of the left knee joint which had been swollen for over a month Microfilariæ were found in fluid aspirated from the joint It was presumed but not definitely determined that *Onchocerca volvulus* was the infecting parasite

In Guatemala we did not observe a single instance o hydrocele or elephantiasis as a complication In the regions in which onchocerciasis occurs in Guatemala other forms of filariasis were not encountered Obviously if the onchocercal parasites should block and cause lymphatic obstruction for example in an extremity and bacterial infection supervene elephantiasis might well follow However in the great majority of cases the onchocercal parasite evidently comes to rest in the more superficial tissues The numerous authoritative reports from Africa mentioned above show that elephantiasis sometimes occurs in that country in association with onchocercal infection

Ocular Lesions

Robles (1916) first called attention to the ocular complications in cases of onchocerciasis in Guatemala His observations were confirmed and extended shortly afterwards especially by Luna and Calderon In Mexico the lesions of the eyes have been studied more recently by Ochoterena, Torroella and Silva, and in Africa by Hissette (1932), Bryant (1935), d Hooghe (1935), and in Guatemala and Africa by the writer

The ocular disturbances generally have an insidious onset In the early stages conjunctival hyperæmia especially near the margin of the cornea, is sometimes present In some instances iritis beginning at the pupillary border, is first noticed in others small areas of opacity in the cornea were observed. These areas may increase in size and become confluent Vascularization of the periphery of the cornea frequently occurs in such instances In a number of cases synechiæ occur and the pupillary reflexes are lost In many of the cases photophobia is complained of These changes cause the discomfort usually incident to conjunctivitis and iritis. In addition, in a varying number of those infected varying in different localities from $\frac{1}{2}$ to $12\frac{1}{2}$ per cent (see section on Prevalence of Ocular Complications'), the eye changes may progress to blindness

Histological studies show that in the bulbar conjunctivæ the lesions present, especially near the margin of the cornea, are in some respects similar to those seen in sections of the skin, though often they are not so severe A more or less marked perivascular proliferation often is present, and there is infiltration with endothelial leukocytes Small groups of small round cells, polymorphonuclear leukocytes and plasma cells may be present also While the microfilariæ are often found in the adjacent fields of the microscope or in another portion of the same microscopical field as that in which the small groups of leukocytes are situated the microfilariæ often are absent among these small groups of cells, and it seems evident from their staining properties that the parasites generally were alive and moving from place to place at the time the tissue was fixed, hence as might be expected in some instances there is no evidence of a reaction in the tissue immediately surrounding the microfilariæ

In the cornea in some areas especially near the periphery vascularization has occurred The capillaries in places are dilated, and among the newly formed capillaries there is infiltration with leukocytes and occasional fibroblasts Perivascular infiltration is present also and in places separation of Descemet's membrane is apparent The epithelium on the surface of the cornea in some cases is irregular, being thinned or destroyed in some areas and in others hyperplastic Infiltration with leukocytes may be present between Bowman's membrane and the substantia propria Bowman's membrane may be folded and

separated in places, and leukocytes and an occasional mast cell and fibroblast may be seen between it and the epithelium In some of these areas newly formed capillaries likewise are visible In the iris perivascular infiltration also is often observed together with œdematous areas infiltrated in places with leukocytes

In the cornea the microfilariæ are found scattered in the anterior portions, particularly in spaces in the tissue which they apparently create by their movements and in the lymph and newly formed perivascular tissue spaces They have been found in the iris particularly near the corneal margin and in the region of the optic nerve

Hissette who gave the first description of the ocular lesions produced by the parasite in Africa has also observed general uveitis with degenerative lens changes also discrete retrobulbar optic neuritis with microfilariæ in the internal and external sheaths of the nerve

Bryant (1935) who has recently made a study of Sudan blindness ' in the Anglo Egyptian Sudan believes the condition to be due to *O volvulus* Clinically the condition gave the ophthalmoscopic appearance of a diffuse retinochoroiditis with optic atrophy often with sclerosis of the retinal vessels and the deposition of masses of pigment on the retina He remarks that perivascular reaction so characteristic of onchocercal keratitis was not present and the cornea was not vascularized as in keratitis but there was considerable vascularization of the retina

Movements of Parasites in Eyes — Muhlens and Hissette have reported that some of their patients attacked with ocular disturbances have complained that they could see before their eyes the movements of the parasites In some of Hissette s patients these movements were compared with and said to resemble the movements of mosquito larvæ in water To one patient they appeared to be black in color to another as worms of fire Hissette believes these symptoms were probably due to a localization of the larvæ in the neighborhood of the retina and of the choroid near to the macula zone Silva with Gullstrand s ophthalmoscope has reported that he had been able to observe in the vitreous humor shadows of the moving microfilariæ

Prevalence of Ocular Complications — The prevalence of ocular complications apparently varies considerably in different regions In southwestern Mexico Larumbe (1926) reported that in Chiapas of 4 000 cases of onchocerciasis about 800 had developed keratitis iritis choroiditis and 100 were totally blind

Hoffmann (1930) in the report of his studies also made at Chiapas does not give the percentage of onchocerciasis with disturbances of the eyes but says that it is evidently high However Muhlens (1932) writes that at La Granja Chiapas about 10 to 20 per cent had ocular disturbances Fulleborn

(1931) found ocular complications relatively seldom among the cases of onchocerciasis he saw in Guatemala No studies of the eye tissues were made In Guatemala among our onchocerca cases, disturbances of the eyes were encountered in only about 5 per cent Hissette, in the northwest Congo, found disturbances of the eye very high In the village of Ilebo, of 150 persons, 68 had disturbances of the eye due to the onchocercal infection, 15 (10 per cent of the population) were blind, 42 of the 68 with disturbances of the eye had nodules upon the head D Hooghe, in the examination of 3 448 Africans, found that 2 1 per cent presented ocular complications, and that 0 4 to 0 5 per cent had become blind However in the very great majority of his cases, nodules were situated upon the trunk, the number of fibromata upon the scalp being only 5 7 per cent

Obviously it would be wrong to conclude because microfilariæ are merely present in small number in the bulbar conjunctiva that the disturbances of the eye are necessarily due solely to the filarial infection It should be emphasized that in many cases of onchocerciasis the microfilariæ in the skin may not produce any disturbance of moment So also in the eye the mere presence of a small number of microfilariæ in the bulbar conjunctiva may not give rise to any lesions of the eye that are demonstrable In many tropical countries disturbances of the eyes are common for various reasons, the individuals being predisposed to such affection through their low degree of intelligence, their poor knowledge of hygienic conditions and their general mode of life

Elliot in his book ' Tropical Ophthalmology", writes that it is very difficult for anyone who has not actually lived the whole year round in a tropical country to appreciate the influence of heat, wind and dust in connection with the production of ocular disturbances Xerophthalmia may also be responsible for such blindness, particularly when associated with bacterial infection Gordon (1933) has emphasized this fact in studies made in East Africa

In one of our cases with microfilariæ in the sections of the eye, an infection with diphtheroid bacilli apparently also played a role in the modification of the lesions It is conceivable that the inflammatory condition produced by the microfilariæ might bring about more favorable conditions for the development of the diphtheroid bacilli in the neighboring tissues Disturbances of the vision due to trypanosomiasis and to arsenical poisoning often are encountered in some regions where onchocerciasis prevails

Diagnosis

The onchocercal tumors sometimes may be confused with dermoid cysts, lipomata, non parasitic fibromata and especially with juxta articular nodules Van Hoof (1926), Sharp (1927) Blacklock (19-7) and the writer (1930) have

emphasized that onchocercal tumors simulate very well juxta articular nodules and frequently affect the same regions also that it is frequently impossible to distinguish clinically one from the other without microscopical examination

The diagnosis of onchocerciasis may be made by puncture and aspiration of fluid from the nodular tumors and the discovery of the microfilariæ in such fluid Often several hundred parasites may be found in a single drop of the aspirated fluid On the other hand no microfilariæ may be obtained even though the nodule is onchocercal in nature Sometimes only adult male parasites or only female parasites or dead parasites are present in the tumor If the microfilariæ are not present in such fluid frequently they may be found in small sections of the skin removed by a safety razor blade In fact in a given series the examination of the section of the skin may give a higher percentage of positive findings than the examination of puncture fluid from the nodules Most favorable results usually are obtained with skin removed from somewhere near the tumor If the tumor is on the scalp the cheek is a favorable place The portion of skin should be transferred to a glass slide and a few drops of normal saline solution added and a coverslip placed over it No teasing of the skin is necessary It is preferable that the sections of the skin should be sufficiently thin so that practically no blood is drawn in making the section

In instances in which no nodules are found detection of the microfilariæ in sections of the skin or of the conjunctivæ is the only satisfactory means we possess for the diagnosis of onchocercal infection However if no microfilariæ are found in the skin it does not exclude the diagnosis of onchocerciasis since they are sometimes absent in the skin when true onchocercal nodules are present In the great majority of cases whether ocular lesions are present or absent the microfilariæ may be detected in thin section of the bulbar conjunctiva obtained with curved eye scissors Diagnosis may sometimes be accomplished in an endemic center by the microscopical examination of the contents of the gut of a simulium fly immediately after it has fed upon an infected patient Microfilariæ sometimes may be encountered in the fly often in considerable numbers even when the direct examination of a section of the skin has been negative The fly in feeding apparently causes a concentration of the microfilariæ at the point of the bite

Immune Reactions

Attempts to demonstrate any immune reactions in onchocerciasis have not been very successful The writer tried to ascertain if hypersensitive reactions could be obtained with an aqueous or alcoholic antigen prepared from the adult parasites or from tumors containing the adult parasites and enormous numbers of ova and microfilariæ Such antigens were employed in performing both an

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PROGNOSIS

There is general agreement in the recent observations of Larumbe Hoffmann Mühlens and Hissette with reference to the ocular lesions only occurring as late disturbances and only usually after the infection or nodular lesions have persisted for some 5 or 6 years or more

The idea previously expressed by some early observers that the removal of the onchocercal cysts resulted in the disappearance of ocular disturbances and a return to normal vision has been shown by many recent observations to be incorrect especially through the observations of Hoffmann Muhlens Torroella Silva Hissette and ourselves The removal of the nodules however with the adult forms if there are no other concealed adult parasites remaining reduces the number of microfilariæ circulating in the tissues of the eye and may arrest the ocular lesions but if anatomical changes have already occurred obviously removal of the nodule may have no perceptible favorable influence Larumbe called attention to the fact that the amelioration of the ocular symptoms frequently occurred but sometimes for only 2 or 3 days following the operation and after this period the ocular symptoms again became aggravated Hissette has observed that this temporary improvement in many cases does occur and he suggests that the temporary improvement in the symptoms may be an allergic response due to the onchocercal antigen set free in large amount by the traumatism which results from the operation

A number of the early reports in which the restoration of eyesight or an improvement of vision was believed to have occurred immediately following the removal of the tumor are perhaps not so difficult to understand when one considers the low degree of intelligence of many of the Indians among which the disease prevails and their superstitious and impressionable nature Especially if the idea were suggested to them that their vision had been improved by the operation they would generally be inclined to agree with such a suggestion. In Guatemala among many of the Indians in the infected districts there is a feeling that removal of the tumors does improve the ocular conditions Especially does there exist the belief that the tumor after a time is likely to lead to ocular disturbances and to blindness This is one of the reasons why the natives are willing and often eager to have the nodules removed and through this circumstance the eradication and control of the disease is made more practicable in Guatemala

Whether a toxin secreted by either the adult parasites or the microfilariæ is responsible or to what extent such toxins are responsible for the ocular lesions has not yet been conclusively demonstrated The ocular lesions probably are incited by the presence and movements of large numbers of microfilariæ in the tissues and the perivascular infiltration results perhaps in a somewhat similar

intradermal test as well as the precipitin reaction with the serum of cases of onchocerciasis in Guatemala Both these reactions were found to be of practically no value in diagnosis While in the majority of instances of onchocercal infection an intradermal reaction was obtained, a similar reaction was also frequently obtained in control cases with no onchocercal infection, and some onchocercal cases gave a negative reaction The precipitin reaction was positive in a few, but negative in many of the cases

Rodhain and Dubois have performed the intradermal test in 3 cases of onchocerciasis in Africa, using an antigen prepared from *Onchocerca volvulus* and *Loa loa* or *Dirofilaria immitis* They state that the reaction is evidently a group one Although positive reactions were obtained in the three onchocercal cases, they did not show the uniformity obtained by them in *Loa loa* or *Dipetalonema perstans* infection

Fulleborn (1931) also prepared an antigen by drying a nodule excised from a case of onchocerciasis The inoculation of this antigen in two cases with onchocerca nodules gave typical wheals, but not only with them, but also with onchocerca free controls sensitive to ascaris and strongyloides antigens

Fairley (1931) using a dirofilaria antigen states the skin test and complement fixation one were both partially positive in one case of onchocerciasis after removal of the nodule Also, Rodhain and Van den Branden in onchocerciasis cases obtained no favorable results with the complement fixation test, using a *O volvulus* extract for antigen, while Montpellier and Beraud with such an antigen obtained 50 per cent of positive reactions in cases evidently not infected with onchocerca

Also Gutierrez in Mexico prepared an antigen made of portions of onchocerca parasites extracted from nodules and performed the complement fixation test Positive reactions were obtained in all cases suffering from onchocerciasis and also from syphilis and ' mal del pinto ' cases He concludes that until this source of error has been eliminated, the reaction can have no diagnostic value in onchocerciasis

Hoffmann and Vargas state that by using an antigen of Gutierrez they obtained a more marked skin reaction in controls in white people not infected with onchocerca than they did with infected natives However, Van Hoof (1934), who has employed the method of complement fixation of Calmette and Massol as modified by Mathis and Labougle with an alcoholic extract of onchocerca believes that the test is a definitely specific one D'Hooghe, who has recently employed the intradermal reaction for diagnosis, concludes that in a region where several species of filaria are endemic, or where the inhabitants are almost always carriers of intestinal parasites, the intradermal reaction loses all value for diagnosis of onchocercal infection

weeds, on which the larvæ or pupæ are fixed and by the removal of logs and stones or the scrubbing of them with stiff brushes have all been suggested, but these are not very practicable preventive measures Oiling of streams especially with phinotas oil O Kane has found especially in New Hampshire to offer a certain measure of value for control of simulium In streams or waterways in which fish of value are not present the larvæ may be rapidly killed, and the problem of concentration of the oil in the water does not offer much difficulty

In Africa, where the disease in many localities is not sharply circumscribed and in those in which the rate of human infection and of fly infection is very high *the eradication of the breeding places of the fly in the endemic regions* constitutes the most important problem Eradication of human infection in such districts would be entirely impracticable without the elimination of the fly Such eradication probably can only be accomplished by extensive sanitary engineering projects and by the provision of a modern water supply for the district Such changes as gradually occur in the building of modern residential centers *will result eventually in the gradual extermination of the disease* By such measures the breeding places of the flies will be removed or gradually reduced, and the inhabitants will no longer come into intimate contact with and not be exposed to the bite of such flies

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and the microfilariæ were found to be still abundant in the subcutaneous tissues

An attempt may be made to rid the patient of the microfilariæ, which may persist after the removal of the tumors, by the use of filaricidal substances Experiments have revealed that several drugs, that might be employed for treatment in man, effectively destroy the microfilariæ in vitro Among these are tartar emetic fouadin and plasmochin Tartar emetic has exhibited the most filaricidal effect in these experiments Fouadin is weaker in its action, while plasmochin was more effective than fouadin

Successful experiments have been reported recently by Wright and Underwood in the treatment and cure with fouadin of *Dirofilaria immitis* infection in dogs It is not at all likely that the adult onchocercal parasites in man, so well protected by their structure and located in the center of the tumors will be destroyed or even unfavorably influenced by treatment with such substances but tartar emetic fouadin and plasmochin are certainly inimicable to the existence of the microfilariæ

Torroella and Silva (1932) subsequent to the Guatemala work recently have called attention to the value of plasmochin in arresting ocular symptoms Torroella has injected a 1 1000 solution into the anterior chamber to replace the aqueous humor They assert that this leads to the death of the larvæ in the cornea Silva states that with the corneal microscope he has observed the death of the parasites to occur following such treatment

In cases in which after removal of the tumors, together with the adults contained in them the microfilariæ persist in the skin and do not disappear under treatment with plasmochin tartar emetic or fouadin, a careful search should be made for small nodules beneath the skin In some instances with persistence of the microfilariæ it is clear that adult parasites may still be present, concealed somewhere in the tissues giving rise to large numbers of new larvæ If large numbers of microfilariæ are still present, the patient should be regarded as a dangerous carrier and be isolated or removed to a region where simulium does not occur until the parasites diminish or disappear through treatment

In localities in which the disease is sharply circumscribed, as in parts of Guatemala the eradication of the human foci of infection is most important However protection from the bites of simulium and destruction of simulium is most desirable both in Guatemala and especially in other countries where the disease prevails In Guatemala the eradication of simulium concerned in transmission in the endemic areas is very difficult for its breeding places are so widely distributed in practically every flowing stream of water in the neighborhood, and such streams constitute the only water supply of the districts Eradication of the flies through attempting to destroy the larvæ and pupæ in the streams by changing the vegetation along the banks, by cutting and raking

CHAPTER XLII

INTESTINAL FLAGELLATES AND CILIATES OF MAN

By WILLIAM C BOECK

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CHAPTER XLII

INTESTINAL FLAGELLATES AND CILIATES OF MAN

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Introduction

The part played by the intestinal flagellates in the production of disease of human beings has always been an uncertain one, especially during the period prior to the World War. During the World War and since, additional knowledge of these intestinal protozoa has been gained from many investigations; new organisms and new methods of treatment have been discovered, and many experimental data have been accumulated with the net result that the relationship of these parasites, broadly interpreted, to human disease has become a more interesting and perplexing problem than ever before.

The investigations made during the World War and for several years following its close were conducted by various trained protozoologists and physicians who completed numerous protozoan surveys, not only on soldiers but on various persons of the civilian population in England, France, Germany, the United States, Egypt, and somewhat later in China, Sweden and Finland. The most outstanding result of these studies was the surprising revelation of a world wide distribution of intestinal parasites with a higher incidence of infection found among the persons examined than ever before was suspected. This observation was brought to the attention of the medical profession at once and has accounted not only for a renewed interest in these organisms, so far as they may be accountable for various intestinal disturbances, but in addition to these, certain other gastroduodenal symptoms, disease of the gall bladder and systemic conditions manifested by such states as neurasthenia, melancholia, asthenia, lack of ambition, loss of "pep" and pathologic changes such as are seen in arthritis deformans have been attributed to these intestinal protozoa.

Before considering the pathogenicity of these parasites and the measures designed to eradicate them, it is essential to mention their names and zoological position, methods for their detection, their morphology and biology, and their geographical distribution.

Nomenclature

The nomenclatorial status of these protozoan parasites is not a settled one and I shall employ, therefore, only those names concerning which there is little difference of opinion and which are in common but not universal use. For those interested, a detailed discussion of the nomenclature for these organisms is given

by Dobell and O Connor[40] Kofoid[83], Boeck and Stiles[16] and more recently by Wenyon[146]

The more common intestinal flagellates of man are *Giardia lamblia Trichomonas hominis Chilomastix mesnili* and the less often encountered flagellates *Pentatrichomonas ardin delteili Tritrichomonas fecalis Tricercomonas intestinalis Enteromonas hominis* and *Embadomonas intestinalis* Besides these, the closely related species *Trichomonas buccalis* from the mouth and *Trichomonas vaginalis* from the urogenital tract also will be given consideration A consideration of the parasitic ciliates, *Balantidium coli Balantidium minutum* and *Nyctotherus faba*, will follow that of the flagellates

All of these organisms are members of that division or subkingdom of the whole animal kingdom known as the Protozoa This subkingdom in turn is divided into four subdivisions each known as a phylum and each differentiated from the other by certain biologic and morphologic characteristics The name of the phylum to which the flagellates belong is called Mastigophora because they all possess long whip-like processes for organs of locomotion The various flagellates differ from each other and therefore it became a necessity for purposes of clas ification to create further subdivisions known as genera and species The first name in the scientific designation of any animal is the genus to which it belongs and the second name is its species Eight recognized genera occur among the intestinal flagellates of man

The intestinal ciliated parasites of man belong to the phylum Ciliophora and only two genera Balantidium and Nyctotherus are recognized All these organisms possess fine hair like processes called cilia for organs of locomotion Table I illustrates the classification of the flagellates and ciliates parasitic in man

TABLE I

CLAS IFICATION OF THE INTE TINAL FLAGELLATES AND CILIATES OF MAN

(MODIFIED AFTER DOBELL AND O CONNOR 1921)

Sub kingdom	Phylum	Genus	Species
		Giardia	*lamblia*
		Trich onas	*ho n s*
		Pe tatri homonas	*ardin delteili*
	Mastigophora	*Tritrichomonas*	*fecal s*
		C i l n a t x	*mesnili*
		Tricercomonas	*in test alis*
Proto oa		*Embadomonas*	*i test nalis*
		Ent omonas	*hominis*
		Balantidium	*c li*
	Ciliophora	*B la t di n*	*m nutum*
		Ny t therus	*faba*

METHODS OF DETECTION

Examination of feces is still the chief and perhaps most reliable means for the detection of the intestinal flagellates and ciliates of man. Certain English and American investigators contend that such examination can be done only by persons who have had much experience in this work and who are familiar with the morphology of the protozoa. This contention is justified to the extent that persons unfamiliar with the use of the microscope never may acquire any skill in the examination of the feces for these organisms, but, on the other hand, I am certain that persons, who know how to use the microscope properly, and who will familiarize themselves with the distinguishing characteristics that separate these organisms from each other, with some study and practice can identify them with much certitude. Certainly it is less difficult to identify intestinal flagellates and ciliates than it is to differentiate motile parasitic amebas. It is not necessary here to go into details of the examination of the feces, for those who desire such details the directions given by Dobell and O'Connor[4] and Boeck and Stiles[16] may be consulted. I shall consider only the careful preparation and the microscopic examination of a thin smear of the feces which must be learned by all who search for these protozoa.

Examination of Fecal Smear Preparations

The person suspected of harboring intestinal protozoa should take either a saline cathartic or some laxative containing bile salts, and the stool should be examined as soon as possible after it has been passed. Stools obtained in this manner yield more evidence of infection than do other stools. The catharsis also obtains a more representative specimen of the colonic contents, and, in the case of *Giardia Lamblia*, may bring down also some of these flagellates from their habitat in the duodenum and jejunum. In fluid or soft stools obtained in this way the flagellates and ciliates are more active and therefore detected more easily. The organisms will be found viable and active in recently passed and warm stools, but they die soon in specimens that have been allowed to stand for a few hours and become cold.

A small amount of feces is rubbed up on a glass slide in a drop or two of physiologic sodium chloride solution, care being taken not to have the preparation so thick as to prevent proper transmission of light through it when viewed with the microscope. A properly made smear, after being covered with a number 1 cover slip, will have a "reading opacity," by which is meant that degree of translucency through which ordinary newspaper print is barely visible.

Differential staining of such preparations has been found of distinct advantage in identifying the motile organisms and their cysts from debris in the fece

For this purpose it is best to make one preparation by emulsifying a small bit of feces in a drop of eosin solution of a concentration 1 1 000 in distilled water or physiologic sodium chloride solution In such preparations the flagellates and ciliates and their cysts do not stain whereas the debris becomes pink Movement of the motile organisms is detected and studied easily and the cysts stand out as refractive unstained bodies on a pink background One is able to tell at once whether cysts are present or absent The cysts of *Giardia lamblia* are identified easily in preparations stained with eosin but it is necessary to employ a strong solution of iodine in staining another preparation to bring out the internal structure of the other motile and encysted organisms and in order to count the number and position of the flagella of the flagellates The solution of iodine is made up from equal parts of distilled water and a 5 per cent solution of potassium iodide saturated with iodine The smears are made by rubbing up a small bit of the feces in a small drop of the iodine solution and then covering it with a cover slip

The microscopic examination should be made with the use of the high dry (4 mm) objective and the 1 inch (number 10) eye piece For the more detailed observation of the manner of locomotion of the protozoa position of the nucleus number and position of the flagella and other structures the oil immersion lens frequently is required

In most cases the solution of eosin and iodine used in separate preparations will enable one to diagnose all the intestinal flagellates and other intestinal protozoa of man if one is acquainted with the morphology of the organisms Sometimes however it is necessary to make preparations stained with iron hematoxylin to get an accurate idea of their structure and for the purpose of permanent record This is especially necessary when there is any question about the diagnosis made from the study of the preparations stained with eosin and iodine For a description of the method one may consult Dobell and O Connor[4] Boeck and Stiles[16] Craig[4] Stitt[131] and texts on clinical pathology

At least two smear preparations from each stool submitted always should be examined before an opinion is given Dobell[41 4] and other investigators have stated that one should examine six stools from the same subject each of which should be negative before deciding that the subject is free from any protozoal infection The negative results of the examination of one stool are not sufficient to prove that the subject is free from parasites because the protozoa of infected persons do not occur in *all stools* *It seems sufficient however* if three such examinations of stools by saline catharsis are negative The procedures for the examination of fecal smear preparations may be summarized as follows

1 A saline cathartic or laxative containing bile salts is administered to the patient and the specimen is collected and examined while it is still warm

2 At least two preparations of reading opacity are made for each stool

The first preparation is stained with eosin solution If results are negative, then a second eosin stained preparation is examined If the results of examination of either the first or second eosin stained preparation is positive, that is if it contains refractive bodies or motile forms, another preparation stained with the solution of iodine is examined to study morphologic details

3 If it is not possible to identify protozoan parasites in the iodine solution, a number of preparations are made to be stained with iron hematoxylin

4 If possible three stools are examined before a person is called normal or uninfected, provided, of course, that the results of all examinations were negative More than one examination should be made in all cases, if there is strong suspicion that protozoa are present

Cultivation of Intestinal Flagellates and Ciliates

This procedure has been made easy, and Hegner and Becker[68], and Kessel and Mason[81] have shown that the attempt to cultivate intestinal flagellates from stools which were found negative for protozoa in the examination of smear preparations, is a valuable procedure, because frequently additional flagellate infections were discovered that otherwise would have escaped detection Although such a practice involves more time, it is essential, if one wishes to feel that the best additional procedure has been employed, to determine the presence of intestinal flagellates in the feces

At present, there are several types of mediums for the cultivation of intestinal flagellates of man The first successful medium in which the intestinal flagellates of man would grow for months, if frequently transplanted into fresh mediums was introduced by Boeck[9] for the culture of Chilomastix This was modified later and became known under the name of 'L E S' medium[13] Other mediums have been devised substituting Ringer s solution for the Locke solution and diminishing the amount of glucose in the solution The serum citrate medium of Tanabe Hegner and Becker and the ovomucoid medium of Hogue have proved successful also The directions for the preparation of some of the more commonly used mediums are given

L E S medium (Boeck)

1 Four eggs are washed brushed with alcohol and broken into a sterile flask containing glass beads From 50 to 100 c c of Locke s physiologic solution then are added and this mixture broken by shaking

2 Test tubes are then filled with a sufficient quantity to produce slants from about 1 to 1 5 inches in length on coagulation by heat

3 The tubes are slanted in an inspissator and heated to 70 C until the egg mixture has solidified then the tubes are transferred to the autoclave and sterilized for twenty minutes at 15 pounds of pressure

4 Into each tube is introduced a sufficient amount of a fluid mixture composed of

eight parts of sterile Locke s solution and one part of sterile inactivated human blood serum so as to cover the egg slant completely The tubes are incubated over night to determine the sterility

5 The Locke solution is made up as follows

Distilled water	1 000 c c.
Sodium chloride	9 0 gm
Calcium chloride	0 2 gm.
Potassium chloride	0 4 gm
Sodium bicarbonate	0 2 gm
Glucose	2 5 gm

The solution is sterilized either in the Arnold sterilizer or the autoclave according to the ordinary methods Some investigators have found it advisable to diminish the amount of glucose to only a tenth of that given others omit it and some (Dobell and Laidlow) substitute rice starch for it

When not sterile human serum may be diluted with Locke s solution to be used and then filtered through a Berkefeld candle filter (Number N) which removes the bacteria

L E A medium (Boeck and Drbohlav[16]) This medium is as succes ful in the cul ture of intestinal flagellates as is the L E S medium It differs from the L E S medium by the substitution of crystallized egg albumin for the human serum A 1 per cent concentration in Locke s solution is employed The medium is sterilized by passage through the Berkefeld candle filter and then added to the tubes containing the egg slants which are prepared by directions given for the L E S medium

Both the L E S and the L E A mediums have been altered in another respect by the substitution of Ringer s solution for Locke s solution by Drbohlav

Serum saline citrate medium Thi successful medium for the cultivation of intestinal flagellates was devised in the Department of Medical Zoology of the School of Hygiene and Public Health of the Johns Hopkins University Its composition is

Sodium chloride	0 7 gm
Sodium citrate	1 0 gm
Loeffler s blood serum (dehydrated)	0 5 to 1 0 gm
Distilled water	100 c c

To this medium Tanabe has seen fit to add the white of an egg (2 c c to each 100 c c of distilled water) because he claims it has a powerful bactericidal action

Ovomucoid medium (Hogue) This medium has been successfully employed for the cultivation of Trichomonas Chilomastix and Embadomonas and is prepared as follows

1 The white of one egg is placed in a flask containing glass beads and the egg albumin is broken by shaking

2 One hundred cubic centimeters of 0 7 per cent sodium chloride solution is added to the flask which again is shaken

3 The fluid is heated in a hot water bath for half an hour keeping it constantly in motion by shaking the flask

4 It is filtered then through cotton cloth with a suction pump

5 Six cubic centimeters is placed in each test tube and sterilized in the autoclave for twenty minutes at 15 pounds of pressure

Cultivation of *Balantidium coli* was accomplished successfully by Barret and Yarbrough in a medium composed of 0 5 per cent sodium chloride 15 parts and human serum 1 part Hegner[3] modified this medium by substituting Ringer's solution for the 0 5 per cent sodium chloride solution The sodium chloride of Ringer's solution was also reduced below that of the standard Ringer's solution The medium contained the following ingredients

Sodium chloride	6 5 gm
Potassium chloride	0 14 gm
Calcium chloride	0 12 gm
Sodium bicarbonate	0 20 gm
Sodium phosphate	0 01 gm
Distilled water	1 000 c c

Eighteen cubic centimeters of thi olution was placed in each test tube and autoclaved after which c c of either human or horse serum and a sprinkle of rice starch were added The cultures were kept in an incubator at 36 C

Morphology and Biology

I have the utmost confidence in the ability of most physicians, who understand the use of the microscope and who keep up the practice of study and of observation by this means, to detect the common and larger intestinal flagellates and the ciliates of man by the methods described In addition, however, they should become familiar with the distinguishing characteristics of structure that separate these parasites from each other This task is not difficult in the case of the flagellated protozoa because each varies from the other as to type of locomotion size and shape of body position and number of flagella and other structures within the body and because their cysts are characteristic for size shape and contents The task is even easier with the intestinal ciliates which because of their comparatively large size, readily attract the attention of the observer and are identified at once or if necessary after staining with the solution of iodine

Many physicians are unable to take more time than that which is required to look at the smear preparations stained with eosin and iodine solutions If they have laboratory assistants they can spend more time making iron hematoxylin preparations for permanency and for the study of details of structure It seems most important therefore that I emphasize in my description of these parasites their appearance when alive in the physiologic sodium chloride solution or the eosin stained smears referring to their size shape and type of locomotion and then describe the additional details that may be seen in the forms killed and stained in the iodine smear preparation Appropriate drawings will be submitted in order to illustrate the appearance of these protozoa when alive when stained with iodine solution and when in preparations stained with iron hematoxylin A description of the finer morphologic details is omitted, but

they may be obtained by referring to the publications of Dobell and O Conner Boeck and Stiles Hegner and Taliaferro Craig[31] and Wenyon[146]

Intestinal Flagellates

Giardia lamblia Stiles 1915 —The chief synonyms are (1) *Lamblia intestinalis* (Lambl) Blanchard 1888 (2) *Giardia intestinalis* (Lambl) Alexeieff 1914 and (3) *Giardia enterica* (Grassi) Kofoid 1920 *Giardia lamblia* has for its habitat the duodenum and jejunum of man For this reason it may be procured in large numbers by means of duodenal drainage from persons harboring it It also occurs in diarrheic stools and in stools following saline catharsis It is the only intestinal protozoan of man known to live in the duodenum This flagellate is small (Fig 1 *a b c*) varying from 9 to 21 μ in length and shaped like half of a longitudinally bisected pear The thicker end is the anterior extremity and the pointed end is the posterior extremity The plane surface is the ventral aspect of the flagellate and the convex surface is the dorsal aspect The convexity also is chiefly limited to the anterior three fourths of the body The ventral surface is not entirely flat but anteriorly a cup like depression known as the sucking disk occurs by which the organism attaches itself to the intestinal epithelium This sucker organ occupies the broader anterior third of the

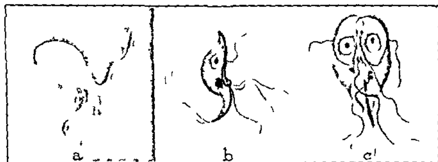


Fig 1 *Giardia lamblia* motile forms (after Dobell from Dobell and O Connor 1921) *a* unstained appearance during locomotion *b* side view *c* ventral view stained with iron hematoxylin (x 000)

ventral surface and is distinctly visible during locomotion and serves to identify this flagellate (Fig 1 *a*) During life these flagellates are seen to move forward in a zig zag path dipping downward then rising upward and rotating on their long axis The rotation brings the sucking disk into view with each turn of the body The progression is effected by means of eight flagella occurring in four pairs each pair composed of a right and left member since they occur on opposite sides on the ventral surface It is difficult to see all these flagella when the organism is alive but they are visible in preparations stained with iodine

In the preparations stained with iodine other structural details are visible Two dark brown stained oval areas the nuclei are seen lying in the protoplasm dorsal to the sucking disk A midrib or rod extends down the middle of the body from the

sucking disk to the end of the tail and there the two caudal flagella originate This midrib or rod seems to be composed of two fibers the axostyles The free ventral flagella arise on the axostyles at a point about one third the distance from their anterior end The posterolateral flagella originate from the distal ends of the posterolateral intracytoplasmic fibrils each of which in turn arises from the axostyle of its side and courses posteriorly and laterally to the margin of the body The sucking disk is surrounded by a supporting fibril that lies in the protoplasm at the margin of the cup and it is joined to the axostyles medially Each one of the lateral flagella arises from either side of the sucking disk Dorsal to the axostyles and across them lies a pennant shaped body staining dark brown in iodine called the parabasal body These details are sufficient for the identification of this flagellate when studied alive or in iodine stained preparations but additional finer cytologic structures are visible in preparations stained with iron hematoxylin as may be seen in figure 1 *b* and *c*

In the examination of most stools submitted the motile forms of Giardia may be less numerous than their cysts The cysts represent the resistant stage of this organism by means of which the infection is transmitted to other cysts following their ingestion in contaminated food or drinking water It is important therefore to learn the distinguishing characteristics of these encysted forms The cysts are ovoid bodies remaining unstained if alive in the eosin stained preparations (Fig 2 *a*) They measure from 10 to 15μ in length and from 6 to 9μ in width Frequently it will be seen that the refractive cytoplasmic body within has shrunk away from the wall of the cyst at one end With in the cytoplasm are to be seen one or more brightly refractive streaks and one or more crescent shaped bodies of similar refractivity

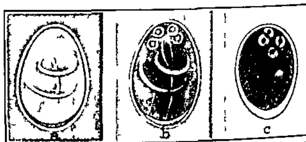


Fig 2 *Giardia lamblia* cysts (after Dobell from Dobell and O Connor 1921) *a* unstained and alive *b* stained with solution of iodine *c* stained with iron hematoxylin (x2000)

In the preparations stained with iodine (Fig 2 *b*) either two or four nuclei may be observed usually at one end of the cyst the longitudinal streaks seen when unstained now are colored deep brown and represent the remains of the axostyles and intracytoplasmic portions of the posterolateral flagella and the fibrils about the sucking disk The crescentic curved bodies are hypertrophied parabasal bodies The cytoplasm generally stains light brown but small cysts that stain a slate shade of blue often may be seen and in them the structural details are not demarcated clearly These forms may represent abnormally developed or degenerating encysted organisms Figure 2, *c* shows the structural details of a cyst stained by the iron hematoxylin method

Giardia lamblia is the only one of the intestinal protozoa of man which has defied thus far all attempts at cultivation in artificial mediums

Trichomonas hominis *Davaine 1860* —The chief synoyms are (1) *Trichomonas intestinalis* Leuckard 1879 ( ) *Trichomonas confusa* Stiles 1902 and (3) *Trichomonas confusa* Stiles and Boeck 1923 *Trichomonas hominis* an inhabitant of the

colon of the human being is a small oval shaped organism varying from 6 to 20μ in length but averaging usually 9 to 13μ in most cases especially when the body is more rounded than oval in shape When very active in the unstained preparations or those stained with eosin and viewed with the oil immersion lens to obtain the best idea of its structure and locomotion this organism is seen to possess an undulating membrane extending from its anterior end backward and often obliquely to the posterior end of the body (Fig 3 a) This undulating membrane is a thin film of protoplasm and possesses a flagellum at its free margin which also rises at the anterior end of the organism This marginal flagellum remains attached to the undulating membrane for its whole length and then extends for some distance beyond the body as a free whip There are also four anteriorly directed flagella which arise at the anterior end of the

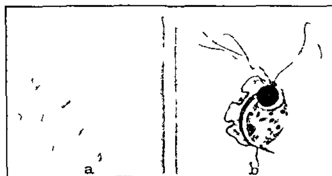


Fig 3 *Trichomonas hominis* motile forms (modified after Dobell from Dobell and O Connor 1921) *a* unstained appearance during locomotion *b* stained with iron hematoxylin (x2000)

body One may see also in the living specimens a sharply pointed hyaline rod protruding from the body for a short distance posteriorly and which may be traced in the cytoplasm to its origin near the anterior end of the flagellate It is called the axostyle A small crescent shaped slit like mouth at the anterior end is visible in the more quiescent organisms

When swimming about these flagellates describe a zig zag course to either side and up and down progressing in a jerky dancing fashion and rotating frequently The jerky movement is brought about by the lashing of its anterior flagella while the rotation is accomplished by the constant wave like movements of the undulating membrane progressing anteroposteriorly When these organisms cease their swimming they become rounded in shape and the movement of the flagella and undulating membrane becomes slower When such individual organisms become chilled or almost moribund the undulating membrane moves so slowly that its movement has been mistaken for the extension of pseudopodia and the flagellate taken for an amoeba In such instances one should look carefully for the anterior flagella and axostyle

In preparations stained with the solution of iodine the trichomonad have been killed and stained and now show additional details of structure The nucleus is a small round or oval dark brown body lying at the anterior end of the organism be

tween the anterior end of the undulating membrane and the slit shaped mouth One also notices a thin darkly stained rod which extends as a line along the base of the undulating membrane no doubt lending support to it It is called the chromatic basal rod by some investigators and the parabasal body by others The axostyle is not stained by the iodine solution and appears as an indistinct hyaline rod beginning at the anterior end of the flagellate and curving gently as it extends to the posterior extremity beyond which a small pointed portion projects The cytoplasm stains light brown and unlike that of Giardia it frequently has several food vacuoles which contain bacteria or cocci and sometimes erythrocytes

The details of structure described and finer ones, are visible also in preparations stained with iron hematoxylin (Fig 3 *b*) The diagnosis of a trichomonas depends entirely on the identification of the motile flagellate as cysts of this protozoan have not been found Therefore warm liquid stools are most suitable for examination and if possible cultivation in one of the artificial mediums described should be done An examination of the culture fluid after sixteen to forty eight hours usually will show an abundance of the organisms

Pentatrichomonas ardin delteili Derrieu and Raynaud 1914 — This trichomonad differs from the species just described in respect to the number of anterior flagella it possesses As its generic name implies it is a trichomonad possessing five anterior flagella (Fig 4) Its dimensions vary considerably as in the case of *Trichomonas hominis* In stained preparations the length varies from 9 to o μ with most forms averaging around 14 μ and the width ranging from 7 to 14 μ and averaging around 10 μ In other structural details *Pentatrichomonas ardin delteili* resembles *Trichomonas hominis*



Fig 4 *Pentatrichomonas ardin delteili* motile form lateral view (after Kofoid and Swezy 1923) stained with iron hematoxylin (x2000)

Tritrichomonas fecalis Cleveland 19 8 — This is another species of trichomonad flagellate of man reported by Cleveland It is of unusual interest because it was maintained in a culture medium composed of feces diluted with sterilized tap water for three years and was transmitted to frogs and tadpoles in which it maintained itself indefinitely In size it is perhaps slightly smaller than *Trichomonas hominis*, its length varying from 6 to 1 μ in stained preparations (averaging 8 5 μ) and averaging 5 7 μ in width (Fig 5) It possesses three anterior flagella and in addition an axostyle an undulating membrane nucleus and mouth as in other trichomonads A noticeable difference is the extremely long axostyle which extends an unusually long distance beyond the end of the body also a characteristic of *Trichomonas augusta* of the frog Cleveland also thought the anterior flagella of this species were probably longer than those of other trichomonads of man and that one anterior flagellum was thicker and longer (from 20 to 40 μ) than the other two which are thinner and shorter (from 18 to 25 μ) The character of the axostyle in this species and the number of anterior flagella are adequate criteria of differentiation from other trichomonads of man

It has been a question whether *Trichomonas hominis* always possessed four anterior

free flagella or whether it might at times have only three Kofoid and Swezy[2] rigidly maintained that the common trichomonads of the human intestine urogenital tract and mouth all have four anterior free flagella and failure to find more than three is either because the fourth flagellum lies hidden from view or because of too inexpert ness in analysis of the specimens It seems likely that this criticism is unwarranted since competent investigators have observed trichomonads from man with only three anterior free flagella and these forms have been assigned to the genus and species *Trichomonas hominis* In view of Cleveland's investigations a trichomonad with three anterior flagella does occur in man and it may be better policy now to classify such forms in the new genus *Tritrichomonas fecalis* and to restrict those trichomonads with four anterior flagella to the genus *Trichomonas hominis* and those with five anterior free flagella to the genus *Pentatrichomonas ardin delteili*

Chilomastix mesnili (Wenyon) Wenyon ff 191 —The chief synonyms are (1) *Ma*

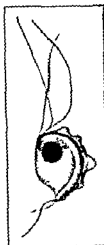


Fig 5 *Tritrichomonas fecalis* motile form (after Cleveland 1928 stained with iron hematoxylin (x2000)

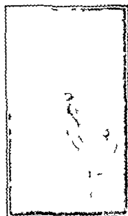


Fig 6 *Chilomastix mesnili* motile form appearance during life motion unstained after Dobell from Dobell and O Connor 1921) (x 000)

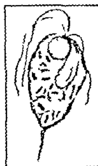


Fig *Chilomastix mesnili* motile form dorsal view stained with iron hematoxylin (after Boeck 192) (x2000)

crostoma mesnili Wenyon 1910 and ( ) *Chilomastix davainei* (Moquin Tandon) Kofoid 1920 This organism is the largest of the flagellates living in the colon of man It usually varies from 8 to 14 μ in length but some larger forms may measure 21 μ in length (Figs 6 and) It is piriform in shape with a broad well rounded anterior end which gently tapers off to a long pointed posterior spine like extremity This spine like tail is used as an organ of attachment and when it is stuck into some of the fecal debris the flagellate bobs up and down or from side to side and rotates frequently When an organism so attached is studied it is observed that there are three anterior free flagella contracting in a wave like and stroking manner There is

tween the anterior end of the undulating membrane and the slit shaped mouth One also notices a thin darkly stained rod which extends as a line along the base of the undulating membrane no doubt lending support to it It is called the chromatic basal rod by some investigators and the parabasal body by others The axostyle is not stained by the iodine solution and appears as an indistinct hyaline rod beginning at the anterior end of the flagellate and curving gently as it extends to the posterior extremity beyond which a small pointed portion projects The cytoplasm stains light brown and unlike that of Giardia it frequently has several food vacuoles which contain bacteria or cocci and sometimes erythrocytes

The details of structure described and finer ones are visible also in preparations stained with iron hematoxylin (Fig 3 *b*) The diagnosis of a trichomonas depends entirely on the identification of the motile flagellate as cysts of this protozoan have not been found Therefore warm liquid stools are most suitable for examination and if possible cultivation in one of the artificial mediums described should be done. An examination of the culture fluid after sixteen to forty-eight hours usually will show an abundance of the organisms

Pentatrichomonas ardin delteili Derrieu and Raynaud 1914 — This trichomonad differs from the species just described in respect to the number of anterior flagella it possesses As its generic name implies it is a trichomonad possessing five anterior flagella (Fig 4) Its dimensions vary considerably as in the case of *Trichomonas hominis* In stained preparations the length varies from 9 to 20 μ with most forms averaging around 14 μ and the width ranging from 7 to 14 μ and averaging around 10 μ In other structural details *Pentatrichomonas ardin delteili* resembles *Trichomonas hominis*


Fig 4 *Pentatrichomonas ardin delteili* motile form lateral view (after Kofoid and Swezy 1923) stained with iron hematoxylin (x2000)

Tritrichomonas fecalis Cleveland 1928 — This is another species of trichomonad flagellate of man reported by Cleveland. It is of unusual interest because it was maintained in a culture medium composed of feces diluted with sterilized tap water for three years and was transmitted to frogs and tadpoles in which it maintained itself indefinitely In size it is perhaps slightly smaller than *Trichomonas hominis* its length varying from 6 to 12 μ in stained preparations (averaging 8 5 μ) and averaging 3 7 μ in width (Fig 5) It possesses three anterior flagella and in addition an axostyle an undulating membrane nucleus and mouth as in other trichomonads A noticeable difference is the extremely long axostyle which extends an unusually long distance beyond the end of the body also a characteristic of *Trichomonas augusta* of the frog Cleveland also thought the anterior flagella of this species were probably longer than those of other trichomonads of man and that one anterior flagellum was thicker and longer (from 0 to 40 μ) than the other two which are thinner and shorter (from 18 to 25 μ) The character of the axostyle in this species and the number of anterior flagella are adequate criteria of differentiation from other trichomonads of man

It has been a question whether *Trichomonas hominis* always possessed four anterior

alone The ability to recognize them is important in the diagnosis of an infection The cysts measure from 6 to 10μ in length and are ovoid except for an elevation at one end which gives them the resemblance of a lemon The wall of the cyst is thickened *where the peculiar knob like elevation occurs When unstained the cysts* appear brightly refractive and show no internal structure except a few more brightly refractive granules (Fig 8 *a*) When seen in preparations stained with solution of iodine (Fig 8 *b*) the cytoplasm stains lemon yellow and at times contains a dark mahogany-colored area a glycogen mass At one side the nucleus appears as a refractive ring within which are one or more granule Remains of the fibrils of the mouth are present beside the nucleus in practically the same position they occupied in the motile organism The recognition of lemon shaped cysts of the dimensions before mentioned and the structures within is sufficient to identify them as *Chilomastix mesnili* Preparations stained with iron hematoxylin enable one to study the internal structure in more detail but they are not necessary for any diagnostic purpose (Fig 9)

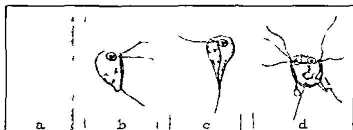


Fig 10 *Tricercomonas intestinalis* motile forms *a* unstained (modified from Wenyon and O Connor 1917) *b* side view *c* ventral view *d* dividing form (after Boeck 1924) stained with iron hematoxylin (x2000)

The next three intestinal flagellates are not prevalent so commonly as are those just described They have been known only since the protozoan investigations conducted during the World War and have been seen by very few investigators on rare occasions since

Tricercomonas intestinalis Wenyon and O Connor 1917 —This very small flagellate is believed to be an inhabitant of the colon Because it is so small it is difficult to determine the details of its structure It measures from 4 to 10μ in length and from 3 to 6μ in width. It is piriform in shape when either its dorsal or ventral aspect is seen but may be rounded when quiescent It possesses a flat ventral surface and a convex dorsal surface seen in figure 10 *b* which is a side view of this flagellate Its anterior end is rounded while the posterior end is drawn out into either a blunt or pointed tail.

During locomotion this organism may be seen to mold its body into all manner of shapes as it passes through minute spaces between small particles in the preparation Its body is one of the most plastic of all the flagellates These organisms move along bobbing up and down and from side to side and often turning over and over either to

no axostyle or undulating membrane as in the trichomonad flagellates As the organism rolls over a large narrow mouth may be seen which begins at the anterior end and at one side (left) as a shallow depression and extends posteriorly for a distance equal to a third to a half of the length of the body The end of the mouth is deeper than its anterior portion and represents a pouch within the cytoplasm This mouth has a right and left lip each supported by a deep lying fibril that may be seen easily in the specimens stained with hematoxylin (Fig 7) The margins of the lip are supported further by a finer fibril running circuitously around the mouth but this also is visible only in specimens stained with iron hematoxylin The lips of the mouth are mobile and movement is both contractile and expansile Within the mouth lies a

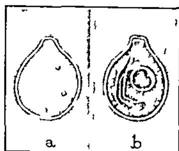


FIG 8 *Chilomastix mesnili* cysts *a* unstained and *b* stained with solution of iodine (after Dobell from Dobell and O Connor, 1921) (x2000)



FIG 9 *Chilomastix mesnili* cyst stained with iron hematoxylin (after Boeck 1921) (x2000)

flagellum down which wave like contractions move continuously These contractions are rapid in active flagellates but often are slowed in moribund specimens and then the flagellum appears to be attached to the inner membranous lip thus forming an apparent undulating membrane within the mouth (Boeck[9]) Some investigators hold however that this flagellum never forms an undulating membrane in the mouth but is always free

When Chilomastix is swimming freely in the medium of the preparation it progresses slowly and deliberately with none of the jerky dipping movement of the trichomonad flagellates It rotates on its long axis but its course is not straight ahead on a single plane such as a bullet describes in its early period of flight but it moves through several planes in a cork screw fashion This is accomplished by virtue of the asymmetry brought about by its large mouth and the presence of a spiral groove in the body which begins anteriorly and runs from right to left (Fig 7) The body is held fairly rigid during locomotion It does not round up when quiescent as do the trichomonads

This form is cultivated easily in any of the mediums described in the foregoing and cultures from stools often show the presence of Chilomastix when examination of the smear failed to reveal it Cultivation is therefore a valuable measure when searching either for Trichomonas or Chilomastix in stools

The cysts of Chilomastix may be present along with the motile forms, or may occur

beyond This flagellum is thicker than the other is directed anteriorly and moves more slowly in its stroking action The movements of the two flagella produce a jumpy or jerky type of progression somewhat resembling that of Tricercomonas from which however it is easily distinguishable by the presence of its mouth and only two flagella

In preparations stained with the solution of iodine the mouth and flagella are distinguished easily and a small round nucleus containing a large central chromatic granule may be seen in the anterior end of the body The mouth also shows a deep staining fibril surrounding it and lying within its free margin This and the details of the nucleus are seen even better in preparations stained with iron hematoxylin (Fig 12 *b* and *c*) In such preparations each of the flagella may be seen to arise from a separate basal granule lying on the nuclear membrane

The cysts of this flagellate (Fig 12 *d*) are also very small and when unstained measure from 4 5 to 7 μ in length and from 3 to 4 5 μ in width In shape they resemble very small cysts of Chilomastix or the early budding forms of yeast organism frequently seen in the stool but unlike the yeasts they show no internal structure while the yeast cells contain a central vacuole with fluid which stains pink in the preparations stained with eosin

In preparations stained with iodine the cytoplasm stains light brown and contains a small round nucleus with a central granule and the fibrils which probably are the remains of the fibril surrounding the mouth of the motile organism before encystment occurred In this respect these cysts resemble those of Chilomastix but because of their size and the difficulty encountered in seeing their contents even when stained one is not likely to be confused with the other This organism has been cultivated by Hogue in an ovomucoid medium and by Wenyon in a soft agar medium of rabbit s blood It may grow on the other mediums employed for the cultivation of intestinal flagellates

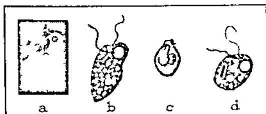


Fig 12 *Embadomonas intestinalis* a unstained during locomotion (original) *b c* motile form stained with iron hematoxylin (after Wenyon and O Connor 1917) *d* cyst stained with iron hematoxylin (after Dobell from Dobell & O Connor 1921) (× 2000)

Enteromonas hominis Fonseca 1915 — The status of this small flagellate which was found by Fonseca [55] in the feces of man is surrounded by considerable doubt chiefly because there have been various dissimilar descriptions by the discoverer himself and by others

The organism was described as oval or rounded and measuring from 5 to 6 μ in diameter (Fig 13) It has three free anterior flagella much longer than the body which arise from a basal granule located near and connected by a finer fibril with the nucleus The nucleus is small and round and contains a large central chromatin mass the karyosome The cytoplasm contains food vacuoles but no other organs Cysts were not found

Dobell and O Connor have suggested that all such flagellates might contain a

right or left. These dancing seemingly purposeless, movements are characteristic of this flagellate. The cytoplasm may show refractive inclusions and there are three anterior free flagella that arise at the anterior end of the organism (Fig 10 *a*). These flagella arise from a basal granule lying near the nucleus which lies also at the anterior end of the body (Fig 10 *b*). A fourth flagellum originates anteriorly from a separate basal granule and runs posteriorly on the flat ventral surface within the cytoplasm finally emerging from the tail of the organism to continue a short distance farther as a free flagellum. The posterior flagellum is contractile and bends actively from side to side or up and down seemingly to direct the course of the flagellate. The anterior flagella beat backward in strong strokes. Sometimes two of the flagella may be stuck together and unless one is careful to notice this one may think there are only two anterior flagella present, one thicker than the other. The tail is often ameboid, and small protoplasmic protrusions of momentary duration constantly alter the contour of the posterior end of the parasite when it is more or less quiescent.

The position and origin from basal granules of the four flagella is difficult to determine in specimens stained with iodine but easier in those stained with iron hematoxylin and viewed with the oil immersion lens (Fig 10 *b* *c* and *d*). The nucleus possesses a distinct nuclear membrane and in its center is a large chromatin granule, the karyosome. The cytoplasm often contains ingested bacteria lying in vacuoles.

The cysts of this flagellate are small ovoid bodies measuring 6 to 8 μ in length and 3 5 to 5 μ in width (Fig 11 *a* *b* and *c*). Unstained the cysts are refractive and show no internal structure. When stained with solution of iodine the cytoplasm stains light brown and some cysts show small dark brown patches which probably represent glycogen. Cysts may be observed containing either one two or four nuclei the structure of which is like that of the nucleus of the motile form. Undoubtedly Tricercomonas is more prevalent than present records would indicate but probably is overlooked frequently because of its small size.

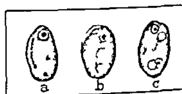


FIG 11 *Tricercomonas intestinalis* cysts *a* uninucleated *b* binucleated *c* quadrinucleated stained with iron hematoxylin (after Boeck, 1924) (x2000)

Embadomonas intestinalis Wenyon and O Connor 1917 — The chief synonym is *Waskia intestinalis* Wenyon and O Connor 1917. This organism is another very small flagellate living in the colon of man which was discovered by Wenyon and O Connor in Egypt during the World War.

When these flagellates are alive (Fig 12 *a*) in unstained preparations or preparations stained with eosin they measure from 4 to 9 μ in length and from 3 to 4 μ in width. They possess a very plastic body and so their shape varies a great deal. Sometimes the body is elongated with a rounded anterior end which on one side seems to project like a hood over the top of the mouth within the cytoplasm while posteriorly the body frequently is elongated gradually coming to a pointed extremity (Fig 12 *a* and *b*) but at times the whole body may be shaped somewhat like an egg. With the oil immersion lens one may observe a single anterior free flagellum making forceful lashing movements and another cystostomal flagellum arising in the anterior end and emerging through the mouth to continue posterolaterally for a short distance

locomotion two nuclei of unequal size referred to as the macronucleus (large nucleus) and the micronucleus (a minute nucleus) lying next to the macronucleus There are also two excretory organs in the form of contractile vacuoles which discharge their contents to the outside through a primitive anus or cytopyge situated terminally at the posterior extremity

Balantidium coli (*Malms n*) *St in 186* — This organism (Figs 14 and 15) is the commonest of the ciliates of man and was discovered by Malmsten in Sweden in the stool of two patients with dysentery Later a similar if not identical organism

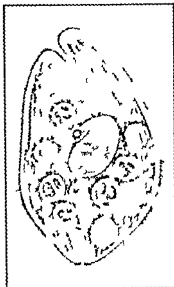


Fig 14 *Balantidium coli* living specimen from feces 1 p … (after Dobell from Dobell and O'Connor 192) (x 000)

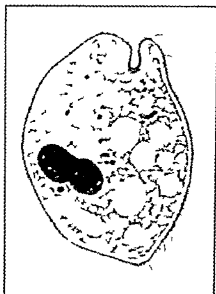


Fig 15 *Balantidium coli* specimen from human stool stained with iron hematoxylin (after Dobell from Dobell and O'Connor 19) (x 000)

was discovered in the feces of swine and it is common belief that man obtains infection by the ingestion of the encysted forms coming from swine Similar organisms have been recovered from monkeys and guinea pigs

Balantidium coli is oval and ranges usually from 50 to 0 μ to 100 μ in length and from 40 to 60 μ in width (Figs 14 and 15) The whole body is covered with short cilia which vibrate with a backward stroke during forward progression of the organism. The anterior end is more pointed than the posterior extremity and just off its center is a funnel shaped mouth extending obliquely into the interior of the body This funnel possesses somewhat longer cilia The parasites move rapidly in rotating manner through the medium of the preparation The body is somewhat plastic and may be compressed while passing between bits of fecal debris Within the cytoplasm large

fourth flagellum which was overlooked and really were Tricercomonas while Wenyon[146] who examined specimens supposed by Chalmers and Pekkola to be Enteromonas discovered they were small rounded forms of *Chilomastix mesnili* in which the mouth was difficult to see More investigation is required before this organism can be accepted as a separate species It has been reported in remarkably few instances this may be the result of its being either overlooked or confused with the commoner flagellates

Craigia Calkins 1913 — The species are *Craigia hominis* Craig 1913, and *Craigia migrans* Barlow 1915 The status of a flagellate originally described by Craig[32] under the name *Paramoeba hominis* and later renamed *Craigia hominis* by Calkins also is unsettled The original description stated that this parasite had both an ameboid and a flagellate stage The ameboid form was similar to that of *Endamoeba coli* and measured from 10 to 25 μ in diameter It developed cysts from which numerous small flagellates escaped Craig s own slides have been examined by Wenyon who stated that they were poorly stained and showed only the presence of typical free forms of *Endamoeba coli* and *Chilomastix mesnili* the latter had never been reported from the Philippines where the preparations were made

Barlow[8] described another species *Craigia migrans* from Honduras but this has not been confirmed by other investigators in the Central American countries

Kofoid and Swezy[83] in 1921 however described a small ameboid oval or elongated flagellate bearing one anterior flagellum and possessing small round uninucleated cysts This organism however does not resemble *Endamoeba coli* in its ameboid stage as Craig stated originally nor do the flagellated forms bear any resemblance to the coarsely tailed organisms that Craig described If this organism represents a true inhabitant of the intestine of man it does not belong to the genus Craigia originally described as the organism seen by Craig The characteristics of the nucleus and the cyst suggest very strongly those of a coprozoic or a free living flagellate and it seems probable that it represents a coprozoic organism and not a true intestinal inhabitant such as Chilomastix

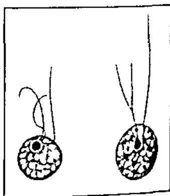


FIG 13 *Enteromonas hominis* motile forms stained with hematoxylin (after Da Fonseca 1915) (x2000)

Intestinal Ciliates

These organisms are found in the stools of man only infrequently in the United States but are more common in Scandinavian countries and South America The task of identifying the intestinal ciliates of man is not so difficult as that of distinguishing the flagellates because they are from five to ten times larger than the latter They also differ radically from the flagellates in several other respects for example they possess fine hair like organs, called cilia for

Nyctotherus faba Schaudinn 1899 — This organism also was isolated by Schaudinn in the case of infestation by *Balantidium minutum* (Fig 18) It has not been reported by any other investigators and for that reason it cannot justly be assumed that it represents a parasitic ciliate of man It is of interest at present only for the purpose of record It somewhat resembles a bean in shape is slightly compressed dorsoventrally and measures from 26 to 28 μ in length and from 16 to 18 μ in width It is covered completely with cilia A mouth extends from the anterior and extends posteriorly to the middle of the body The macronucleus is round about 6 μ in diameter and the micronucleus lies adjacent to it A contractile vacuole is present in the posterior area and a terminal anus is present as in *Balantidium coli*



Fig 18 *Nyctotherus faba* motile form from left side (after Dobell from Dobell and O Connor 1921 after Schaudinn) (x1000)

Distribution

Knowledge of the distribution of the intestinal flagellates and ciliates of man has been increased greatly since 1917 as a direct result of numerous protozoan surveys throughout the world Soldiers of various nationalities children — healthy those ill in hospitals and those in detention homes — adult patients in hospitals or in various social institutions university students and so forth have been examined for intestinal protozoa

In many of these studies comparisons have been made of the incidence of infection of the people of one country with the incidence of people of other countries In such studies the results are not strictly comparable for there are many circumstances surrounding the examinations that should be considered These are methods used in examining the stools the experience and skill of the investigators the nature of the stools whether cold or fresh and warm and whether or not obtained after catharsis whether or not cultivation also was employed since more infections with flagellates will be found when this method is used in addition to the examination of smears and furthermore the number of stools examined in each case since the rate of infection generally will be higher among persons examined three to six times than among those examined only once

Geographic Distribution

Bearing in mind the matter of examination when it is wished to compare the figures for the rate of infection for the different intestinal flagellates among various persons the world over one is impressed at once by the universality of their distribution for the most part they are not confined to the tropics for

food vacuoles containing ingested matter may be noted There is a definite movement of these food vacuoles from the anterior end where they are formed to the posterior end By the time they reach the posterior end digestion has been completed and the end products are excreted through the anus There are two contractile pulsating vacuoles one situated to one side anteriorly and the other to one side near the posterior end Thomson and Robertson believe that these two vacuoles are connected by a fine cytoplasmic duct and that the posterior vacuole discharges into the anal canal In this way excretory products find their way to the exterior

In specimens stained with the solution of iodine the details of structure are more clearly shown The large nucleus or macronucleus situated near the center of the ciliate is somewhat bean shaped and in its concave depression lies the minute dotlike micronucleus The cilia also stand out clearly and occur in longitudinal rows over the whole organism It never is necessary to make preparations for staining with iron hematoxylin in order to identify this organism but such preparations are valuable for detailed cytologic study (Fig 15)

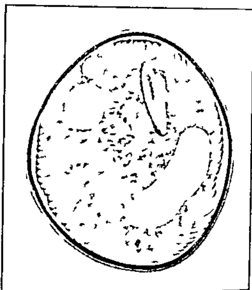


Fig 16 *Balantidium coli* cyst unstained from feces of man (after Dobell from Dobell and O Connor 1921) (x1000)

This ciliate produces round cysts with a thick wall which measure from 50 to 60 μ in diameter (Fig 16) Some cysts contain two individuals probably as a result of the division of the original organism that encysted The cilia both nuclei and often both contractile vacuoles are present in the encysted forms. Sometimes movement of the ciliate occurs within the cyst. These cysts can be identified readily when unstained, but their structure is clearer when stained with the solution of iodine

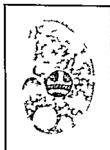


Fig 17 *Balantidium minutum* motile form ventral view (after Dobell from Dobell and O Connor 1921 after Schaudinn) (x1000)

Balantidium minutum Schaudinn 1899 — This is a smaller species of Balantidium and has been reported only on a few occasions Schaudinn first described it in 1899 (Jakoby and Schaudinn) This organism measures from 20 to 30 μ in length and from 14 to 20 μ in width (Fig 17) It possesses a terminal anterior mouth that extends posteriorly like a long groove almost to the center of the body The macronucleus is rounded instead of bean shaped and there is only one contractile vacuole in the posterior end of the organism Little is known about this organism because it seems to be an unusually rare parasite of man

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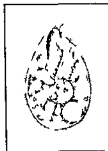


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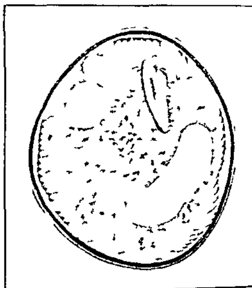


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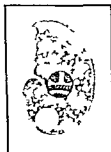


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On the basis of one examination in each case it would appear that *Giardia lamblia* occurs in 3 to 7 per cent of the adult population of the world (table 2) *Chilomastix mesnili* occurs with about the same frequency In most surveys only a few cases of Trichomonas infection were found the reason for this is that most of the stools were not fresh when examined and the trichomonads had died or if present, they were quiescent and missed detection Kessel and Mason however inoculated cultures with some of the stool to be examined and Trichomonas was found in 5 9 per cent of their series of cases in the hospital Hegner[62] reported an incidence of 0 6 per cent for Trichomonas in 286 hospitalized patients in Central America Other reports also seem to indicate that this flagellate is more common in Central American and northern South American countries than in other parts of the world in which studies have been made although against this is the 12 5 per cent rate of infection with Trichomonas found by Lynch[96] in Texas

A significant feature in all except one of these surveys was the absence of cases of *Balantidium coli* the intestinal ciliate of man. Svensson found two cases among 1 244 patients in an asylum in Sweden and one case among 159 patients in a hospital in Finland There are more references in literature to cases of infection occurring in the Scandinavian and Baltic Sea countries than in other countries of the world Sporadic cases of infection in human beings have been reported from the United States Germany France Russia South America and the Philippine Islands

Race Sex and Age

So far as race and sex are concerned in the distribution of the intestinal flagellates surveys have shown but little difference in the incidence of infection among the white race as compared to that in the negroes in the United States or the Chinese in Peking and practically no difference in rates as regards sex.

There is a marked difference between children and adults concerning infections with intestinal flagellates *Giardia lamblia* is much commoner in children than in adults the rate of infection was unusually high among some groups of children studied In England of 548 children under twelve years of age examined by Matthews and Smith[105] each child examined once 14 1 per cent were infected with Giardia and 1 8 per cent with Chilomastix while Trichomonas was not discovered in any case (table 3) Again at Leeds England Nutt examined 128 children the majority of whom were in a workhouse infirmary Giardia occurred in 39 8 per cent and Chilomastix in 7 8 per cent of these cases Most of the children were examined only once Nutt also examined 533 adults during the same investigation and found that Giardia occurred in only

practically as high rates of infection prevail in the temperate zones, even in Sweden and Finland, as in Egypt or Brazil Table 2 illustrates the universality of distribution of the three commoner flagellate infections

TABLE II

INCIDENCE OF INTESTINAL FLAGELLATE INFECTION DISCOVERED IN VARIOUS PROTOZOAN SURVEYS

Protozoan Surveys	Persons examined	Percentage of Infection			Average number of examinations in each case
		Giardia	Trichomonas	Chilomastix	
English civilians (Dobell) 1921	3 146	9 3		2 9	1+
United States troops and civilians (Boeck and Stiles) 1923	8 029	6 5		3 1	1 6
Chinese hospital cases (Kessel and Svensson) 1924	816	7 8	2 2	3 4	3 1
English dysenteric convalescent patients (Matthews and Smith[1] *) 1919	4 068	9 9		3 0	3
California civilians (Kofoid) 1926	6 834	5 2	2 6	6 6	3 3
Hospital cases Los Angeles California (Kessel and Mason) 1930	2 731	4 4	5 9	8 3	3
Sweden hospital cases (Svensson) 1928	611	5 1		0 9	1
Finland hospital cases (Svensson) 1928	159	6 3		0 3	1
Central Americans (Hegner) 1925	86	2 1	20 6	7 7	1
Brazil soldiers (Young) 1922	251	6 3		3 8	1
Egyptian cooks (Wenyon and O Connor) 1917	87	7 0		1 1	1
English troops from France (Mackinnon) 1918	1 233	13 4		5 0	5 7
English troops from Greece Syria and so forth (Mackinnon) 1918	447	13 6		5 1	5 7
United States home service troops (Kofoid and Swezy) 1920	576	6 4	0 5	3 5	1+
United States foreign service troops (Kofoid and Swezy) 1920	2 300	5 7	0 1	4 2	1+
United States home service troops (Boeck and Stiles) 1923	2 584	6 0		3 1	1+
United States foreign service troops (Boeck and Stiles) 1923	3 536	5 5		1 5	1+
Texas civilians (Lynch) 1928	1 040	2 3	12 5	1 5	1?

It is surprising to find reports of Giardia infection in very young infants In England Nutt found Giardia present in six children aged three weeks and three nine, eleven and twelve months respectively Maxcy found a child aged twenty two months infected with Giardia Zahorsky[134] recently reported ten cases of infection among children aged from four to twenty four months It is not uncommon to find other children in the same family harboring *Giardia lamblia*

Among adults there are fewer cases of Giardia infections and more cases of Trichomonas infections and especially of Chilomastix This may be seen by comparing the figures in tables 2 and 3 although some exceptions also occur At Washington D C (Boeck and Stiles) among a group of 300 children and 02 adults each of whom was examined six times Giardia occurred in 3 per cent and Chilomastix in 3 per cent of the children while Giardia was present in 4 4 per cent and Chilomastix in 10 8 per cent of the adults

Trichomonas too seems more prevalent among adults than children It is conspicuously absent in the observations of most protozoan surveys among children an exception is the 2 per cent incidence found among 50 Chinese children studied by Kessel and Svensson Lynch[96] reported 12 5 per cent. among patients examined in Texas Hegner[62] reported 20 6 per cent among the natives of Central America and Kessel and Mason reported 5 9 per cent among patients in Los Angeles In the latter study however cultivation was employed as a routine and as mentioned before this accounts for the higher rate of infection than that of most other surveys in which the smear examination was the only method of detection used

Institutional Distribution

The rate of infection for all the intestinal protozoa among either children or adults in institutions for mental diseases detention homes for orphans and those requiring disciplinary care is much higher than that among children and adults not so confined This was pointed out by Boeck and Stiles who drew attention to the extraordinarily high rate of Giardia infection among children so confined (as high as 50 6 per cent) and Chilomastix among the adults (16 3 per cent) Chilomastix infections seem to be unusually prevalent among adult patients in other asylums too for Matthews and Smith[10] reported 23 3 per cent in England Thomas and Baumgartner reported 21 0 per cent in New York and Svensson reported 0 5 per cent in a Swedish asylum Boeck and Stiles stated that the rate of infection for these protozoa afforded a satisfactory sanitary index of the institution for with poor sanitary provisions closer contacts and poor personal hygiene the rate of infection is higher than in other institutions in which sanitation is excellent personal hygiene is encouraged and

3 4 per cent, Chilomastix in 11 4 per cent and Trichomonas in 0 3 per cent of the cases

This also was the experience of American investigators in the United States (table 3) Maxcy reported 18 per cent of 89 children infected with Giardia in

TABLE III

INCIDENCE OF INTESTINAL FLAGELLATE INFECTIONS IN CHILDREN

Protozoan Surveys	Persons examined	Percentage of Infection			Average number of examinations in each case
		Giardia	Trichomonas	Chilomastix	
Liverpool infirmary (Matthews and Smith) 1919	548	14 1		1 8	1
Leed infirmary (Nutt) 1921	128	39 8		7 8	1 +
Training school A Washington D C (Boeck and Stiles) 1923	329	14 5		3 3	5 2
Training school B Washington D C (Boeck and Stiles) 1923	83	50 6		1 2	5 5
Mixed group schools A and B (Boeck and Stiles) 1923	300	23 0		3	6
Hospital Baltimore (Maxcy) 1921	89	18 0			2
Hospital Boston (Boeck) 1927	50	22 0			2 2
Chinese orphanage (Kessel and Svensson) 1924	50	28 0	2 2	8 0	6
Hospital Peking China (Kessel and Svensson) 1924	50	20 0		2 0	3 to 6

the Harriet Lane Hospital of Johns Hopkins Hospital neither Chilomastix nor Trichomonas was found Boeck[14] found 22 per cent of 50 children at the Children s Hospital in Boston infected with Giardia, no other protozoa were found Boeck and Stiles reported 50 6 per cent of 83 children in Training School 'B for children in Washington D C and 14 5 per cent of 329 children of another training school infected with Giardia whereas Chilomastix was present in 1 2 per cent and 3 3 per cent in each group respectively Most of these children were examined six times In China Kessel and Svensson found 28 per cent. of 50 Chinese children in an orphanage infected with Giardia, 2 per cent with Trichomonas and 8 per cent with Chilomastix Each child was examined six times In another group of 50 Chinese children, 20 per cent were infected with Giardia and 2 per cent with Chilomastix, while Trichomonas was not discovered

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practiced, and close personal contact is avoided This was well illustrated by the very low rate of infection for all intestinal protozoa among inmates of a state prison, in which sanitary and hygienic measures were excellent, as compared with the high rate of infection present in two training schools and one asylum in Washington, D C, in which more personal contact was permitted personal hygiene was poorer general sanitary measures were less effective and infected food handlers were present

United States Army

There has been an impression in the minds of the medical profession and in layman that many of our United States troops, who were in active service in France and in other countries abroad during the World War, acquired new protozoan infections as a result of mingling with soldiers from other and from tropical countries, and from living in trenches under extremely unhygienic conditions at times In this country, the investigations of Kofoid and Swezy[57] at New York seemed to show this to be true for the *Endamœba histolytica*, which produces dysentery This however, was neither substantiated by the investigations of Boeck and Stiles in 1923 nor later by Riley in 1929

The conclusion reached by Boeck and Stiles was that, as a body, the United States soldiers who had been abroad, represented no greater source for the spread of amebiasis than did the troops that remained at home, this contention also appears to be true for flagellate infections since Giardia and Chilomastix occurred as frequently among both groups (table 2) both in the surveys of Kofoid and Swezy and of Boeck and Stiles, Riley s figure of 5 per cent for *Giardia lamblia* infections also is in agreement Table 2 shows a rather uniform rate of infection for the flagellates the world over, taking into consideration the number of examinations made for each person The higher rates of infection that exist among certain classes of the population are doubtless due to the presence of poor sanitation and unhygienic practices rather than to climatic conditions

DISSEMINATION OF INFECTIONS

The dissemination of protozoan intestinal infections is a matter for public health consideration It involves the problem of the proper and prompt disposal of waste from human beings since fecal contamination of food and drinking water is responsible for the spread of these infections The motile forms of the intestinal flagellates and ciliates with the exception of Trichomonas probably play but little part in the spread of infection since they do not live long outside the human body These protozoa with the exception of Trichomonas, possess resistant stages known as cysts and the ingestion of these encysted organisms is accountable for the origin of new infections

The cysts are present in the feces of infected persons and are surrounded by a firm wall or membrane which protects the living organism within from unfavorable conditions outside the human body Desiccation is unfavorable to these encysted organisms and after subjection to drying they soon die Hence those in a moist or liquid environment live longer and if the medium is comparatively free of fermentative or putrefactive processes the cysts may be viable for a long time Cysts of Giardia were found apparently viable by Boeck[11] at the end of thirty two days and those of Chilomastix at the end of one hundred eighty seven days in stools which had been washed several times with several changes of water to remove the coarse debris and soluble coloring matter then covered with tap water and kept at 1 to 2 ° C But cysts remaining in stools without any moisture other than that of the stool will not live as long because the bacteria are more numerous and their products of metabolism exert a lethal influence on the cysts In trying to determine the thermal death point of these cysts Boeck[10] found that not all the cysts of Giardia were killed until they had been subjected to a temperature of 64° C for five minutes and those of Chilomastix to 7 C for the same length of time The spread of infections of Giardia and Chilomastix is enhanced when the cysts are ingested as soon as possible after their passage through the body before they have been subjected to any heat or dryness and when the feces in which they lie has been diluted by water

There are several methods of dissemination The sequence of contaminated fingers to mouth or to food and drink probably accounts for most of such infections This easily explains infections in unsanitary homes among crawling infants and young children whose habit it is to put everything they touch in their mouths Parents and other children in the family may be instrumental in encouraging new infections through unhygienic personal practices resulting in the contamination of food water and other articles placed in the mouth This explains the tendency for several members of the family to harbor similar infections Likewise infected food handlers also constitute a means of spreading these infections in the home and especially in institutions One such food handler in an institution in Washington D C was found to harbor five different protozoan infections

Flies undoubtedly play a significant role in the spread of these infections Wenyon and O Connor discovered that the cysts passed through the intestine in an apparently unaltered state in flies that had fed on infected feces Root found that in the intestine of flies that had fed on infected feces cysts of Giardia apparently were viable and unchanged up to sixteen hours and Chilomastix cysts up to eighty hours The cysts remained viable for even longer should such flies be drowned in water It is more than likely that flies coming from unclean toilets to food or alighting on the face and lips of infants and chil

dren are responsible for many new infections The outdoor toilet is certainly a menace in spreading all protozoan infections wherever such exist in rural communities and in poorly sanitated villages (Boeck)[1]

Since cysts of Trichomonas have not been discovered, infections by this organism must occur following the ingestion of the motile flagellate It passes through the stomach and on to the large intestine where it establishes itself The organisms remain viable in moist stools for a long time, and for several days when water is added Trichomonas is not destroyed by passage through the intestine of the fly (Hegner)[65], and it is quite probable that flies also spread this infection by contaminating food and drinking water

The spread of infections of *Balantidium coli* probably is accomplished by very much the same means as are the flagellate infections Since domestic swine and guinea pigs harbor a Balantidium morphologically identical with the species found in man, it is more than likely that these animals constitute the chief source of infections in human beings Strong showed that many persons with this infection had had intimate association with swine Infection might occur following the ingestion of food and water contaminated by fecal matter containing the cysts of this ciliate No doubt flies play a part in the contamination of the food and water used, especially on farms, where they may feed on swine dung and later fly to the kitchen and deposit infected droppings in moist food, and in the drinking water or milk left uncovered

Within recent years, much study has been made of the intestinal parasites of monkeys, swine cats and rats this has led to the belief held by some authorities that these animals may be reservoirs for human infections because the protozoa in their intestines are morphologically indistinguishable from those of man Boeck[8] reported a species of Giardia from white rats used in a laboratory in California that morphologically was identical with *Giardia lamblia* of man Its size and structure were within the same limits This similarity has been reported by other investigators and the question arises of its identity with *Giardia lamblia* Hegner[64] was able to obtain a temporary infection in rats with *Giardia lamblia* from man the organisms were found in the ileum of the rat which was the same place that infection occurred with the species reported by Boeck Is it possible that the form Boeck discovered was in reality *Giardia lamblia* or did Hegner only discover the same Giardia in his rats and not *Giardia lamblia* which he fed the rats? In the future it may be shown that the Giardia from the rat may be transmissible to man and be identical with *Giardia lamblia* Wenrich and Yanoff[144] were able to infect rats with the Pentatrichomonas of man They believe that the Pentatrichomonas of rats and man are identical and that the rat may be the source for this comparatively rare trichomonad infection in man

Monkeys harbor amoebas flagellates and balantidia identical with those

found in man Some of these parasites have been transmitted to kittens and rats, and some intestinal forms of human beings have been transmitted to mon keys Brumpt showed that the Balantidium of monkeys is infective for swine while the Balantidium from swine has been transmitted to monkeys by Walker[112] The intestinal protozoa of the monkey that resemble those of the human intestine may be shown to be identical with the species of man and the monkey may represent an additional animal reservoir

The pig besides being a probable source of human infections of *Balantidium coli*, also may be a probable source for human infections of Chilomastix since the report by Kessel[80] of a species identical with that of man

Summarizing it may be stated that man most commonly is infected following the ingestion of the cysts with the exception of Trichomonas in which case no cysts are known and the motile form is infective Dissemination is obtained by the part played by fingers directly and food handlers and flies indirectly in contamination of human food and drink with infected fecal matter For this reason personal hygiene domestic and institutional and rural and urban sanitation for the proper disposal of waste from human beings is most desirable and necessary

Pathogenicity of the Intestinal Flagellates

During the middle of the eighteenth and nineteenth century it was a natural procedure on the part of physicians to examine the feces of patients who were suffering from dysentery and diarrhea with the hope of finding the etiologic agent of the gastro intestinal disorder The result of such examinations ac counts for the discovery of most of the inte tinal protozoa of man The commoner flagellates Giardia Chilomastix and Trichomonas and the ciliate *Bal antidium coli* were discovered in advance of the parasitic amoebas but with the exception of Balantidium observations of importance to the medical profession were not attached to these organisms until after the discovery by Losch in 1875 of an amoeba (*Endamoeba histolytica*) which later was shown to be the *cau e of amœbic dysentery*

Following this it seemed only natural to suppose that since one of the in testinal protozoa of man was proved to be the cause of a distinct disease (amoe bic dysentery and its complications) all the other protozoa were probably pathogenic But Walker and Sellards in 1913 proved that man harbors one pathogenic amoeba *Endamoeba histolytica* and one harmless amoeba *Endamoeba coli* infection with the latter never has caused symptoms recognizable of any disease These investigators proved by the inoculation of human subjects that at least *Endamoeba coli* was truly commensal and furthermore they showed that clinical symptoms were not always present in all the persons infected with

the pathogenic amoeba, *Endamoeba histolytica*, such persons they called "carriers" This was a new concept regarding protozoan infection Walker and Sellards found that the amoeba might be present in its encysted stage in the formed stools and could be transmitted from the carrier to other persons by the ingestion of the encysted organism resulting in the production of either amoebic dysentery, or another carrier

This recently discovered knowledge that both pathogenic and nonpathogenic commensal amoebas existed, and the recognition of the carrier as a definite state of infection subsequently led to a divergence of opinion regarding the pathogenicity of the other intestinal protozoa, especially the flagellates of man There were those, who still believed that all the protozoa were harmful, and when diarrhea was absent, it meant that either these persons were carriers without any symptoms at the time, or that other ill defined symptoms were present but were not recognized by most physicians The physicians especially interested in these protozoa and in gastro intestinal disease constituted the majority of members of this group Then there was the other group, which consisted of most protozoologists and most physicians who believed that with the exception of the amoeba *Endamoeba histolytica* and the ciliate *Balantidium coli*, for which there was definite tangible pathologic evidence of pathogenicity, the other protozoa were not true parasites but commensals or harmless organisms living on the detritus and fluids in the intestine, as in the case of the intestinal protozoa living in animals belonging to the lower mammals and herbivores Their opinion was based on the absence of convincing pathologic and well controlled experimental evidence of pathogenicity They felt that the carrier state did not exist for the flagellates as it does for the amoeba *Endamoeba histolytica*, because the flagellates never were pathogenic

This was the state of affairs up to the beginning of the World War in 1914 From that time up to the present, important discoveries were made which included not only new facts concerning the general biology of the already known protozoa of man, but new members of the human intestinal protozoa were found and described Many protozoa were cultivated in artificial mediums and this permitted even further investigations into the life history of these organisms The discovery of the surprising incidence of infection with the intestinal protozoa among the general population of European countries China and the United States and additional evidence of the part played by these forms of organisms in the production of diarrhea and dysentery, stimulated an increased interest in these protozoa by physicians The attempt was made to link up the presence of all of these organisms not only with disturbances of the bowel but to ascribe to these intestinal protozoa the etiology of chronic disturbances of the gall bladder and certain other chronic diseases (often with extra gastrointestinal symptoms) certain nervous disorders such as neuritis, various forms of neurasthenia and

melancholia, also states of general debility loss of energy loss of weight and arthritis deformans The present attitude of a number of physicians is to regard all the intestinal protozoa as pathogenic organisms capable of producing the symptoms and diseases before mentioned but this point of view is held by a distinct minority The majority of physicians feel that the evidence offered to substantiate such a claim still is insufficient and too unconvincing to warrant any such conclusion Therefore it seems advisable to review critically the evidence to date that concerns the question of pathogenicity of the intestinal flagellates and ciliates

Giardia lamblia

It is difficult at present to be certain whether *Giardia lamblia* represents a member of the harmless commensal group of intestinal protozoa or whether it is a facultative parasite and at times pathogenic Giardia lives in the duodenum and jejunum in which it swims about either in the mucous secretion found in the lumen of the glands or in the lumen of the bowel itself At times it may be seen attached to the epithelium by its sucker Its food probably is derived from the intestinal juices and the food passing along Man is never aware of this robbery of his food and the amount lost represents an insignificant portion of that previously ingested Because of this attachment to the epithelium Giardia is believed by many to cause some harm to man It has been blamed for causing several disease disturbances chief among them being recurrent diarrhea chronic disease of the biliary tract duodenitis and pylorospasm The part played by this organism in the production of diarrhea will be considered first.

Diarrhea — The diarrhea produced by Giardia is said to be characterized by intermittency and several liquid or soft stools daily each containing flocculi or masses of yellowish mucus which under the microscope may contain from a few to a large number of flagellates It is conceded generally that such stools are free from blood although a few references in the literature are to the contrary There may be some cramp-like colicky abdominal pain associated with the diarrhea Between spells of diarrhea there may be regular bowel movements with normal stools or constipation with small hard stools The flagellates do not occur in normal or hard stools but their cysts may be present which is proof that infection does not end with the disappearance of the diarrhea

It has been contended that because the flagellates occurred in the liquid stools they must be the cause of the diarrhea This is an old and false argument however because liquid stools following the administration of a saline laxative also contain motile flagellates It is probably more correct therefore to regard the presence of the motile Giardia in the stools as a result of the diarrhea and that the rapid peristalsis occurring with diarrhea swept the flag

ellates from their home in the upper part of the small intestine through the remainder of the bowel to the outside with the feces, just as occurs after a saline laxative The mere presence of Giardia in the stools of diarrhea does not by itself constitute any evidence of etiologic relationship, and proof must rest on sounder deductions

It has been stated that diarrhea is especially prevalent among children infected with Giardia, but there is no more evidence that this is more true of children than of adults with such infections, and such statements usually leave out of consideration other causes of diarrhea in children

Most Giardia infections occur in children aged from four to seven years. Many cases have been reported in infants and children aged less than four years in England and in the United States In England, Matthews and Smith,[180] after examining 548 children aged less than twelve years, stated "The intestinal protozoa are in no way connected with the occurrence of summer diarrhea in children" In the United States similar conclusions were reached by Maxcy, by Boeck and Stiles, and by Boeck[14] in studies of children from Baltimore Washington, D C, and Boston respectively Zahorsky,[153 154] however, in a study of fifteen infants infected with Giardia, felt that this flagellate produced increased intestinal peristalsis, chronic diarrhea resulting in lessened food absorption and consequent retardation of growth, poor color and flabby tissues But this was not true of all the cases that were cited Opposite conclusions were drawn by Noone Waltz and Donnelly in a much larger series of cases in children They found 16 per cent of 304 children aged less than twelve years infected with Giardia, the youngest was nine months old, and the highest rate occurred among children aged five and six years In this careful investigation to ascertain the relation of Giardia to disease in children these investigators stated Among the children admitted to the hospital who had diarrhea as a complaint or who had a history of having had diarrhea, there was sufficient clinical and laboratory evidence to substantiate diagnoses other than giardiasis In this study no diarrhea was observed, the cause of which could be attributed in the least way to the presence of Giardia , and "no definite symptom nor group of symptoms was observed that could be interpreted as indicating the possible presence of Giardia in the intestinal tracts of the children studied that did not occur more frequently in children whose stools did not contain Giardia

It has been pointed out (Boeck[14]) that diarrhea as a disturbance in children gradually decreases in incidence as they grow older The condition occurs more frequently in infants and in very young children than among children aged five years or more If Giardia always produced intermittent diarrhea, then it would be expected that the incidence of diarrhea would be greater in children aged around six years than among infants and very young children, since Giardia is

more prevalent among the former group Bacteriologic investigations by Davison[36, 37] *Wollstein and others indicate that most of the diarrheas of infants and* young children are due to infections with dysentery bacilli Such bacteriologic studies although necessary are generally absent in cases cited to illustrate the production *of diarrhea by Giardia* The identification of Giardia in the stools of diarrheic children constitutes no evidence per se of the etiology of the intestinal disturbance

In adults there seems even less convincing evidence that Giardia causes diarrhea I (Boeck[14]) have mentioned elsewhere the results of the examination of 3 187 American soldiers of whom 269 stated that they had diarrhea at the time the stools were taken Giardia was present in 6 3 per cent in the group with diarrhea and in 5 4 per cent in the group without diarrhea It was present in 5 1 per cent of the other cases (,8) that had a history of diarrhea and dysentery and in 5 6 per cent of those (6 042) that had no such history The almost identical rates of infection among persons who had diarrhea or a history of it and those who did not have such history would tend to show that the presence of Giardia cannot of itself explain the presence of diarrhea Kessel and Mason have sought to determine the relation of Giardia to colitis but their studies are *not convincing of a causal relationship Hollander stated that his patients with* Giardia infection were constipated and in none was there a history of diarrhea Yet Smithies[1-8] claims that diarrhea always occurred in his patients Physicians are not in general agreement on this subject

It has been stated also that the diarrhea ceased after appropriate treatment cleared up the Giardia infection With the exception of a small number of cases it is improbable that the present methods of treatment succeed in ridding the patient of the infection The treatment stopped the diarrhea but later examinations of the stools showed that the infection was often present

Clinically the case of the relation of Giardia to diarrhea is best summarized by quoting the conclusions of Magath and Brown who recently made a critical study of this question They stated After thorough study of these groups (children and adults infected with Giardia or Chilomastix and control persons without protozoan infestation) diarrhea is probably most often explainable on the basis of improper food or infection with certain bacteria or perhaps some as yet unknown abnormal physiologic state These possible causes are materially strengthened by the self limitation of the symptoms in many cases and by the ability to relieve most of these patients by proper food and general hygienic measures Scientific proof is lacking for maintaining that intestinal flagellates cause diarrhea

Duodenitis —It has been asserted that Giardia causes diarrhea because it produces duodenitis The evidence on which such hypothesis is based is twofold (1) The experimental work of Fantham and Porter and Descheins[39, 40] is cited

to show that, in rats and kittens, duodenitis is set up, which is characterized by localized hemorrhages erosion and ulceration of the mucous membrane blocking of the glandular crypts by the flagellates and production of diarrhea clinically and (2) duodenal drainage, practiced by many physicians, often has revealed the presence of Giardia, many times in countless numbers, in the duodenal contents, they may be seen in flocculi of yellow (bile stained) mucus which came from the glandular crypts often in association with a variable amount of desquamated epithelium and clumps of bacteria This epithelial desquamation was said to be due to a chronic erosive process caused by the flagellate, and duodenitis was considered to be present The case of dysentery reported by Fairise and Jannin, which later came to necropsy is cited also as evidence that dysentery and pathologic changes may be caused by Giardia These observers found motile and encysted Giardia in sections of a large cauliflower growth in the cecum and in ulcers of the colon

It must be stated, however that the work of Fantham and Porter and of Deschiens[39, 40] has not been confirmed by other investigators Simon[126] failed to infect rats with Giardia of man Hegner[64] later thought that he succeeded in doing so but diarrhea or demonstrable pathologic changes of the bowel were not observed Likewise duodenitis or diarrhea did not occur in laboratory rats that harbored a species of Giardia similar to, if not identical with, the species in human beings (Boeck[14]) The erosion of the duodenum noticed by Fantham and Porter and by Deschiens might have been due to manipulation at post mortem examination or to bacterial infection Furthermore, Fairise and Jannin did not report duodenitis or other pathologic changes in the duodenum of their patient at necropsy, where such changes would be expected to occur, if at all The large tumor and ulcers found in the colon were sufficient to explain the diarrhea and subsequent death of the patient, while the Giardia simply were caught in the tumor and ulcers while on their way out of the body It should also be stated that there is no case on record of duodenitis in man that has been attributed to Giardia that was recognized as such either at operation or at necropsy Logically it may be expected that a certain amount of epithelial desquamation occurs normally in the duodenum as in other epithelial tissues of the body, but the evidence that *Giardia lamblia* plays any part in it is inadequate at present Diarrhea is not necessarily a result of duodenal irritation or duodenitis, for it is generally absent in cases of duodenitis or peptic ulcer of the duodenum, which represents much more severe irritation and definite pathologic changes than those ascribed to the flagellates

Pylorospasm — It is argued that Giardia when exceedingly numerous and attached to the epithelium might not only interfere with the absorption of food, but also rob the patient of food This seems like mere conjecture and quite improbable since as many or more flagellates are seen unattached and trapped

in mucus than fastened to the epithelium and furthermore passage of food through the duodenum and upper part of the jejunum is exceedingly rapid and it is probable that the amount absorbed by the flagellates is very insignificant It has been said also that Giardia might emit some metabolic product which when absorbed might prove to be a chemical irritant or poison At present there is no proof to support such a theory Because of its numbers alone it might cause some irritation and according to Van der Reis this would lead to duodenitis with pylorospasm If this were true it seems strange that the symptoms of pylorospasm do not occur in from 10 to o per cent of all children since about that number are infected with Giardia The hypothesis of Wezler that Giardia may be a factor in the production of chronic duodenal ulcer merits a similar criticism

Cholecystitis —Within the last decade has appeared the hypothesis that Giardia may be the cause of chronic disease of the gall bladder This hypothesis was advanced as a result of the practice of duodenal drainage by physicians who attempted in this manner to explain symptoms in the upper part of the abdomen by the examination of the duodenal contents and the bile These symptoms were epigastric fullness or bloating gas in the stomach belching occasional nausea alone or with vomiting pain at the right costal margin or in the epigastrium which sometimes was colicky and at times dull for as long as a few hours but at times there might be only vague discomfort Jaundice might occur occasionally As noted in most cases the symptoms were suggestive of chronic cholecystitis yet they were often sufficiently indefinite and vague to cause some hesitancy in making such a diagnosis

When Giardia was found in the biliary drainage its presence often was sufficient for some physicians to consider it responsible for the disturbances in the upper part of the abdomen There are frequent references in the literature of the United States France and Germany to the presence of Giardia in the B fraction of the bile obtained by duodenal drainage and presumably coming from the gall bladder It is argued that this constitutes evidence that Giardia is present in the gall bladder itself and at once it is assumed the flagellate is responsible for the symptoms Especially does this appear to be a fact it is contended when the Giardia were absent in the fasting duodenal contents, but present in the B bile But the presence of Giardia in the B bile fraction does not mean that the organisms necessarily came from the gall bladder B bile is *obtained after the administration of a hypertonic magnesium sulphate solution* by means of the duodenal tube and as Chiray and Lebon and Boeck[14] pointed out this hypertonic solution acts as an irritant to the duodenal mucosa causing hypersecretion of mucus and increased flow out of the glandular crypts carrying with it mucous flocculi containing numerous Giardia (Fig 19) The B bile mixes with this secretion and hence the Giardia appear in it but they come

from the duodenum That this is true in most cases is borne out by the fact that the large majority of gall bladders removed at operation, with the exception of a few instances, have been free of Giardia Such examples of gall bladders free of Giardia in cases in which these flagellates were present in the duodenum have been reported by Westphal and Georgi, Chiray and Lebon, Silverman, Lyon and Swalm, Wezler, Boeck[14], and Castex and Galan[4 25]

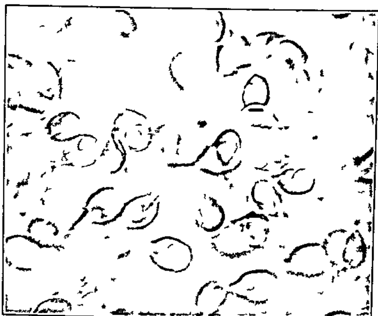


FIG 19 *Giardia lamblia* living motile forms obtained by duodenal drainage (x 00) (Photograph by T B Magath The Mayo Clinic.)

Westphal and Georgi in 1923, reported on several cases of disease of the biliary tract associated with Giardia The studies of Westphal and Georgi have been referred to often by physicians who believe that Giardia cause disease of the biliary tract Westphal and Georgi reported on cases of icterus simplex or catarrhal jaundice and cases of chronic cholecystitis without icterus The catarrhal jaundice cleared up with repeated duodenal drainage, at which time Giardia was discovered Three other patients were operated on and Giardia was not found in the gall bladder however, stones and a small carcinoma of the neck of the gall bladder occurred in one case, a thickened wall in another and in the third case the gall bladder walls were thickened and *Bacillus coli* was recovered in cultures One other patient was observed to have symptoms suggestive of chronic cholecystitis and cholecystectomy was performed A few motile Giardia ere found in a rather thick and stringy sediment from the gall bladder There were no visible signs of any present or previous inflammation of the gall bladder Histologic preparations showed only a plasma cell here and there, and the

muscular coat was only slightly thickened Giardia were not seen attached to the epithelium This case is cited as an example not only of the invasion of the gall bladder, but of the cause of chronic cholecystitis the latter as a cause hardly seems justified in view of the absence of lesions

Smithies[17] also reported finding Giardia in a gall bladder removed at operation and since then he claims to have found it in several other cases in which cholecystectomy was performed No statement of the histologic pathology is given in these cases and one is led to assume that the organisms were found in the contents of the gall bladder It is probable that other factors may have been responsible for the cholecystitis when it existed

As a result of their studies Westphal and Georgi felt that *Giardia lamblia* does not seem to be pathogenic by itself but only a harmless commensal in many cases However in persons with antecedent disturbance of function of the bowel as a result of dysentery toxin endocrine or climatic factors associated with an unusual abundance of Giardia in the duodenum these observers felt that Giardia might act as a co-partner in the production of disease as a result of the irritation caused in the duodenum Furthermore they thought that irritation of the sphincter of Oddi by the Giardia would lead to spasm and stoppage of bile flow and that this stagnation would favor the migration of colon bacilli up the biliary tract and lead to the production of cholecystitis and cholangitis Some of the flagellates might then ascend the common duct to the gall bladder and irritate the mucosa causing increased secretion of mucus and possibly absorption of decomposition products of dead protozoa and help to produce some disturbances or disease of the gall bladder or biliary passages They regarded the pathogenicity of Giardia only as a relative one and it depended on some antecedent disturbance of the bowel in persons of a hypersensitive stimulated personality caused by endocrine imbalance This hypothesis appears to lack conviction because in the absence of definite histologi pathologic change that can be attributed to the flagellates in the duodenum and gall bladder one may go no further at present than to conclude that Giardia may ascend the bile passage to the gall bladder on rare occasions but that there is no pathologic evidence showing that it cause visible injury there

It is therefore difficult at present to ascribe pathogenic properties to *Giardia lamblia* of man since definite and convincing pathologic data are lacking It may be argued that these flagellates might aggravate an already existing pathologic disturbance of the duodenum but it is a point difficult to prove For those physicians who still wish to believe that Giardia may be pathogenic under certain circumstances it must be assumed that in most of the cases it probably is only a harmless commensal and the person a carrier Unfortunately however the carrier state is likely to end abruptly as soon as the subject passes over the threshold of the physician s office who believes that Giardia is always patho-

genic, providing either diarrhea, or upper abdominal symptoms suggestive of chronic cholecystitis is present and providing no attempt is made to study the case from all angles as to the etiology of the disturbance

Trichomonas hominis

Diarrhea and Dysentery — These conditions are believed by many physicians to be caused by this organism The diarrhea is said to be intermittent, often alternating with constipation It is stated to occur in short attacks lasting from one to several days with liquid or soft stools, which are neither typical nor characteristic of any disease In some cases of dysentery, however, in which the stools are liquid and contain mucus and blood, the condition has been attributed to *Trichomonas hominis* and *Pentatrichomonas ardin delteili* Finding flagellates in the stools constitutes the basis for diagnosis, and too often this is the only reason for incriminating these protozoa in the intestinal disturbance

There seems to be an impression among certain protozoologists and physicians that when diarrhea occurs and the trichomonads (or other flagellates) are numerous in the stool they are the cause of the diarrhea With this idea in mind Kessel[79] concluded that persons are carriers when only a few trichomonads appear in the stool, but when trichomonads are found in great numbers in diarrhoeic stools which contain no other known pathogenic microorganisms, there is just as much reason to assume that the trichomonads have brought about the diarrhoeic condition as a result of their cumulative effect (thus finally disturbing the balance relationship between host and parasite) as there is to conclude that the diarrhoeic condition existed first in the bowel and merely formed an environment particularly suitable for multiplication of Trichomonas' It seems that the fallacies of such an argument are several and apparent Barlow[4] noted that trichomonads were more numerous in the stools on the day following the taking of a cathartic than in the first stool obtained after its administration He concluded that the increase in numbers at the time of an intestinal disturbance is a result and not a cause and depends on the more favorable conditions for growth produced by fluid stools This conclusion is substantiated also by the tremendous number of these flagellates that can be obtained in a proper liquid culture medium

Frequently, several investigations are cited as evidence that the flagellates produce definite pathologic changes in the colon Hadley[67, 68] maintained that *Trichomonas gallinarum* was the cause of blackhead in turkeys, but his contention regarding the etiology of blackhead has been disproved definitely

The studies of Escomel[50, 51] in South America are cited frequently as contributing evidence that dysentery in man may be caused by *Trichomonas hominis* It is unfortunate that these have been referred to both extensively and fre

quently because the conclusions are hardly justified This work must be questioned seriously because it is doubtful as to the species of protozoan studied by Escomel He claimed that cysts were observed in cultures and the feces of the dog he had infected but at present protozoologists agree that cysts of Trichomonas have not been observed if they do occur Furthermore photographs of the lesions in the bowel were published but according to Wenyon[145] the appearance of these resembled the changes seen in cases of bacillary dysentery and were not seen in five cases of trichomonad infection noted by him at necropsy Therefore since certain features of these investigations are open to question or other interpretations and since the observations have not been confirmed by others it may be stated that the work sheds little light on the possible pathogenicity of Trichomonas

Another observation however has been referred to as proof of the pathogenicity of these flagellates Wenyon[145] found Trichomonas in the lumen of the colon of five cases at necropsy but in one case some of the trichomonads were found also in the goblet cells of the submucosa however evidence of local inflammation was not observed Although Wenyon felt the invasion was real and not a post mortem phenomenon it is likely that as in the case of the investigations of Hadley on turkeys that the changes represented an artefact in view of the absence of inflammation and because the goblet cells were not invaded in the other four cases Recently the results have appeared of the experimental studies by Kessel[79] on the inoculation of kittens with various trichomonads from man monkeys rats and pigs Diarrhea occurred in the infected kittens and thinning of the wall of the colon was observed with some superficial necrosis and ulceration of the mucous membrane Trichomonads were found in the necrotic tissue and in the lumen of the glands

This work may be cited as evidence that *Trichomonas hominis* may be pathogenic One should however await confirmation of this work with better control measures *Certainly the observations are not similar to those of Wenyon* which Kessel stated they resemble because Wenyon saw no evidence of superficial ulceration and inflammation The observations are more like those of Escomel and may be due to bacterial infection Furthermore clinically and pathologically results similar to those obtained in kittens by Kessel are not known to occur in man Lynch[96] and Zahorsky[143] considered Trichomonas as a harmless flagellate and not responsible for the production of diarrhea and this was the conclusion reached by Tsuchiya in perhaps the most intensive detailed clinical pathologic investigation to date which primarily was concerned in seeking evidence regarding the pathogenicity of *Trichomonas hominis*

He studied thirty patients harboring this flagellate infection from practically every clinical and laboratory point of view as regards the character of the intestinal flora the blood picture gastric acids metabolism intestinal symptoms

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Chilomastix mesnili

Chilomastix has been considered by many physicians to be the cause of intermittent diarrhea. Strangely enough, there is less enthusiasm concerning its probable pathogenicity than that of *Trichomonas hominis*, yet they occur with about the same frequency and if anything Chilomastix is more numerous than Trichomonas in adults. It may be that many cases of diarrhea in which Trichomonas was reported as found were actually infections with Chilomastix since these two flagellates frequently have been mistaken for each other.

There is even less evidence of any pathologic change that might be attributed to Chilomastix than in the case of Trichomonas. Many animals have infections of Chilomastix similar in structure to *Chilomastix mesnili* but there is no evidence of lesions or diarrhea occurring in them. The Chilomastix of the monkey and domestic pig have been considered reservoirs of human infection yet no form of diarrhea is known to occur in them for which flagellates may be held accountable. Kessel[90] claims that he infected young pigs with *Chilomastix mesnili* but diarrhea did not occur and lesions were not found.

Wenyon[140] examined the colon of three persons who were infected with Chilomastix but who had died from other causes. No gross or microscopic pathologic changes occurred that he felt could be considered due to the flagellates. Kessel and Mason found Chilomastix in as many persons with constipation as in those with diarrhea and diarrhea occurred in almost as many persons who were free of all flagellate infections as it did in persons harboring Chilomastix. This would indicate no relationship between the presence of Chilomastix and diarrhea, which conforms with the opinion of Lynch[96] and Magath and Brown[99].

Tricercomonas, Embadomonas and Enteromonas

There is no evidence at present that indicates any pathogenicity on the part of these smaller flagellates of man and like the trichomonads and Chilomastix they may be only commensal organisms living in the human colon.

Systemic Manifestations

Ely, Reed and Wyckoff in 1921 with Kofoid and Swezy[89] made the announcement that arthritis deformans was due to systemic infection with *Endamoeba histolytica* from the colon with subsequent localization in the joints in which the arthritis resulted. This conclusion has not met with general acceptance on the part of pathologists. There have been no experiments to date that would substantiate the claim.

expressed the belief that *Trichomonas vaginalis* is a harmless flagellate living either in healthy or diseased vaginas

Capek reported two cases of purulent anterior urethritis in male patients similar to that produced by the gonococcus which, however, was absent in the smears in which the trichomonads were found He believed that the infection was derived by contact, since trichomonads also were present in the vagina of the wife of each patient Lewis and Carroll reported trichomonads isolated from the urine obtained from the left renal pelvis by ureteral catheters in a male subject with pyelonephritis It seems unlikely, however that the flagellates were solely or even partly responsible for the chills and fever in this case This infection simply represented a rare ascending migration of the flagellates up the urinary tract, probably along with bacteria which were responsible for the symptoms

There is room for much scientific research in trying to determine the true identity of the trichomonads of the urogenital tract, the mode of infection and transmission and their role in the production of any symptoms Certainly the production of characteristic vaginitis still is open to question, and any effort to solve the problem must not fail to consider the influence of the bacterial flora in such a condition

Trichomonas buccalis — This organism lives in the mouth and may be found most frequently about the teeth with recessed gums and in the pus that may be present between the gum and the tooth This pus may be expressed by pressure on the gums Recently Hinshaw[70] and Kofoid[5] stated that *Trichomonas buccalis* never occurs in the normal mouth, but usually is found in advanced cases of pyorrhea or gingivitis and frequently is associated with *Endamoeba gingivalis* These investigators believe that it is quite likely that these organisms have something to do with the production of pyorrhea, but that such a conclusion is not warranted from the results of experiments thus far completed Hinshaw[71] succeeded in infecting dogs with both *Trichomonas buccalis* and *Endamoeba gingivalis*, and noted that striking pathologic changes occurred which closely simulated pyorrhea He added however This experiment was quite inconclusive as to the etiology of the lesions because of inadequate controls At present the relation of *Trichomonas buccalis* to the production of pyorrhea remains unsettled and the problem requires much further investigation It will be difficult to solve since it is almost impossible to find many persons without a slight amount of pyorrhea to serve as normal subjects for control observations As stated in the foregoing, it seems most likely that *Trichomonas buccalis* and not *Trichomonas hominis* is the species found occasionally in the sputum of persons with abscess of the lung or bronchiectasis

few cases, however lesions occurred in the colon Brumpt also noted some ulceration of the colon of pigs infected experimentally Manlove claimed that even when there are apparently no symptoms of colitis in man harboring this parasite definite lesions of the colon may exist that apparently are due to the ciliates



FIG 20 *Balantidium coli* lying in the interglandular tissue (x140) (Photograph by Thomson and Robertson 1921)

Balantidium coli may be regarded as a facultative pathogenic parasite Infection of man therefore falls into two categories First there may be entire absence of symptoms the so called carrier state Second definite colitis with diarrhea or dysentery may exist in some persons the active state of infection and tissue invasion

Carriers are more numerous than persons with colitis and easily may go unrecognized Walker[14] found that of fifty seven cases observed symptoms were not displayed in forty six and Pinto reported another series of eleven cases without symptoms In persons suffering from colitis due to *Balantidium coli*

The idea of the production of systemic effects was extended to include other amoebas of man by Reed, and the same effects previously had been attributed to flagellates by Barrow[6, 7] It was contended that not only the production of chronic arthritis but other symptoms and states of ill health such as melancholia, neurasthenia, lassitude, indefinite abdominal pains and debility, were attributed to the intestinal flagellates Barrow , in a review of 725 cases of protozoan infection, found 535 with Chilomastix Seventy nine patients with arthritis deformans were infected with protozoa, of which 94 cent were Chilomastix, 8 3 per cent Trichomonas, and 2 8 per cent Giardia This is an unusual number of cases of infection by Chilomastix, and Barrow feels that this and other flagellates are significant in the etiology of chronic arthritis, perhaps as a result of the absorption of toxins they liberate or that occur from decomposition of some of the protozoa following death

On the other hand in a similar study by Lynch[95, 96] of 240 persons with intestinal protozoa, none of whom had arthritis, Chilomastix occurred in 7 5 per cent and Trichomonas in 12 5 per cent of the cases He states "To go into a discussion of the systemic effects of such lumen dwellers and of such symptoms as leg weakness and headache leads us into a field of pure conjecture We know nothing about whether they give rise to a poison or, if they do whether it is absorbed He saw no evidence in his study to show any relationship between neurasthenia of persons and the presence of flagellates within them These opinions coincide also with those previously expressed by Barlow[4]

The flagellate as a cause of chronic arthritis and other systemic disturbances has not met with much enthusiasm in the United States or abroad, the evidence for it is not considered convincing, and there is no experimental scientific evidence for its support at present Certainly more data are needed on the metabolism of these flagellates in order to discover what by products may be formed, whether or not these products may be toxins, whether or not they are absorbed, and the effects of such absorption if it occurs

Pathogenicity of the Intestinal Ciliates

Balantidium coli

The balantidia of monkeys, swine and guinea pigs, as mentioned previously, probably are identical with the species found in man Infections in human beings probably originate following the ingestion of cysts from these animals, especially from swine Many experiments on the transmission of these parasites from monkeys to pigs and pigs to monkeys by Brumpt and Walker[12] support this contention In the great majority of these animals neither colitis nor pathologic changes were produced, they represented healthy carriers In a

plug formed from mucus pus fibrin and necrotic tissue In the bottom of the ulcers often lie several balantidia that invade the apparently normal tissue About them is little evidence of cellular reaction There is slight infiltration both by leukocytes and lymphocytes some edema dilated vessels and lymphatics the latter may contain parasites (Fig 1)

It is difficult to determine which pathologic change occurs first the superficial erosion and necrotic process of the formation of ulcers I am inclined to believe that the primary pathologic change is the bacterial invasion with erosion and necrosis of the epithelium and that this process enables the Balantidium to begin its invasion of the mucosa with further cytolysis of tissues and formation of ulcers Excellent and detailed accounts of the pathologic changes of balantidic colitis are given by Bowman Walker de Souza Campos and Dopter

Since all persons with balantidic colitis may have been carriers without symptoms at one time previously it is necessary to institute treatment of all such carriers when they are discovered just as in the case of carriers of *Endamoeba histolytica* the cause of amoebic dysentery and its complications

Treatment of Intestinal Flagellate and Ciliate Infections

The status of treatment of flagellate infections is not satisfactory Chemotherapy has been the method resorted to most frequently with the result that a multiplicity of drugs and methods of treatment have been proposed by almost as many physicians with each one frequently claiming a cure yet too often the same method failed to obtain such result when used by others The term cure has been employed too often to signify that the patient had been rid of his flagellate infection when what it actually represented was an insufficient number of negative examinations The failure of physicians to follow their supposedly cured patients with repeated examinations at infrequent intervals over several months often has led to unwarranted claims for the efficacy of certain drugs in the treatment of the flagellate infections because subsequent examinations often showed that the infection was still present

Giardia lamblia Infections

Undoubtedly certain persons with Giardia have been cured by some form of treatment this might have occurred in spite of the treatment since some of these infections eventually terminate of their own accord otherwise one cannot adequately explain the falling off of the incidence of infection among adults as compared to that of children Thus far however a specific substance has not been discovered which when administered to man can be relied on to eliminate the Giardia

severe diarrhea or dysentery may occur, characterized by frequent liquid or semiliquid stools containing parasites, much mucus, pus and often blood Pus in the stools is a prominent feature The patient generally suffers from colicky abdominal pains and tenderness on palpation over the course of the colon As in all cases of dysentery, there occurs a loss of weight and often emaciation from

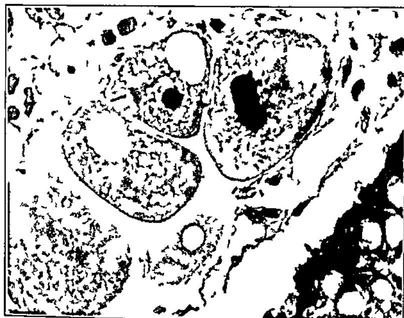


Fig 21 *Balantidium coli* high power view (x,oo) of the group of organisms shown in figure 20 (Photograph by Thomson and Robertson 1929)

dehydration anorexia loss of strength, malaise and at times a slight elevation of the temperature (Fig 20)

The pathologic changes seen in balantidic colitis are somewhat like those seen in amoebic colitis but the extra intestinal complications of the latter are not known to occur Two prominent features are noted First, there is superficial erosion and necrosis of the epithelium, which may be localized in patches or generalized for large areas of the colon Leukocytic infiltration occurs in the tissue being destroyed along with dilated engorged blood and lymph vessels Here and there small hemorrhages occur from destruction of the capillaries and at times fibrin mucus and pus tend to form an overlying scum or pseudomembrane This is the origin of most of the pus seen in the stools and is due to bacterial invasion Second both macroscopic and microscopic ulceration of the colon are present The ulcers with somewhat elevated hyperemic edges with overhanging margins may extend into the submucosa and even involve the muscularis tunica as well They may contain a dark colored necrotic mass or

In later years the two arsenicals, treparsol and stovarsol have been used by many physicians These are given by mouth Castex and Galan[69] feel that they give very satisfactory results Many physicians in America also are employing them I have seen no cures by means of these arsenical compounds but I have been assured by others that they have obtained cures and that the cases were followed up for several months after treatment to make certain that the infection had disappeared It would seem that treparsol and stovarsol should prove at least as efficacious as neoarsphenamine and certainly have an advantage over the latter since they are administered by mouth

Stovarsol is more slowly eliminated from the body than treparsol and continued administration of large doses may lead to toxic manifestations such as exfoliative dermatitis The drugs therefore should be given in courses of several days each with intervals of from four to seven days between courses A convenient method employed by Brown in the treatment of amoebic dysentery at the Mayo Clinic may be tried It consists in the administration of one tablet (0 37 grams) of treparsol three times a day for four days followed by an interval of from four to seven days after which another four-day course of treparsol is given this may be followed by a third or fourth administration after intervening free intervals Patients treated in this way should be examined at various intervals during the next three or four months to make certain that the infection has been cleared up before a cure can be claimed

It must be admitted that to the present any one form of treatment for infections with Giardia has as many or more failures to its credit as it has cures and much more investigation is needed to find a substance that will rid the body of this infection

Trichomonas and Chilomastix Infections

There are more references in the literature to the treatment of infections of Trichomonas than to the treatment of infections of Chilomastix and the small flagellates less frequently encountered It is more than likely that any form of treatment that is efficacious for the eradication of trichomonads from the colon probably would have a similar effect on the other flagellates As many and often similar drugs have been tried in the treatment of these infections as in the treatment of infections of Giardia

Some investigators advocate a standard treatment with emetine and other drugs for all intestinal protozoa Reed and Wyckoff[118] advocated the following course of treatment (1) ten daily hypodermic injections of 0 06 gm (1 grain) of emetine hydrochloride (2) daily doses of 0 2 gm (3 grains) of emetine bismuth iodide to a total of 6 gm (40 grains) (3) three full

The treatment employed for amoebic dysentery with ipecac, or its alkaloid salts, emetine hydrochloride and emetine bismuth iodide, have been tried by many physicians Barrow[71], for example, administered 2 to 4 gm (30 to 60 grains) of ipecac in capsules, each containing 0 3 gm (5 grains), coated with salol keratin each night for six to ten nights, or sometimes 20 mgm (⅓ grain) of emetine hydrochloride was given by hypodermic injection each day for one to two weeks, and often 2 to 8 c c (30 to 120 minims) of the fluid extract of ipecac in 120 c c (4 ounces) of water was given through a duodenal tube This treatment also was used for other flagellate infections Treatment, however, with emetine has not proved satisfactory in most cases The English investigators, Dobell and Low, Wenyon and O Connor, also noted that Giardia infections did not disappear when emetine was given in those cases associated with *Endamoeba histolytica*

Many physicians have advocated the use of thymol, turpentine, salol, methylene blue, carbon tetrachloride, bismuth subnitrate, terebenthene, bismuth salicylate and other compounds for treating infections caused by Giardia None of these has proved to be efficacious

Smithies[129] advocated treatment by daily purgatives of mercurous chloride together with sodium bicarbonate administered late at night, along with 60 c c. of magnesium sulphate solution in the morning for several days De Rivas[140] advocated an intra intestinal thermal method which consists of the administration of 500 c c of hot (from 45 °to 47° C) physiologic solution of sodium chloride by means of a duodenal tube, preceded by the administration of 30 c c. of a 30 per cent solution of magnesium sulphate This was repeated four times No other reports confirming these two methods of treatment have been published, but both physicians claimed good results

Since the work of Yakimoff, Wassilevski and Zwietkoff and later of Kofoid, Boeck, Minnich and Rogers on the use of arsphenamine for ridding mice and rats of Giardia infection the arsenicals have been employed more extensively than other chemical compounds in the treatment of similar infections in man Neoarsphenamine given intravenously in the usual doses has been claimed by some investigators as a specific remedy, and in other hands it has failed It seems probable that this treatment may have proved successful in some cases, since it was efficacious experimentally in rats, but in the latter the dose was many times greater than that given to man figured on the basis of body weight Although Carr and Chandler Simon[15], Kantor and others think this drug was efficacious in their cases such was not the experience of Reed and Wyckoff[137], Silverman and Marcellus, and Hollander claimed to have cured only one of three cases Schill employed an extra measure of treatment in the form of repeated duodenal drainage with a 20 per cent solution of magnesium sulphate added to the administration of neoarsphenamine and claimed a cure by this means

Balantidium coli Infections

Fortunately, fewer drugs and chemicals have been used in the chemotherapy of these infections than in the treatment of flagellate infections and of these ipecac or emetine the arsenicals neoarsphenamine and stovarsol, and oil of chenopodium appear most efficacious

Many experiments by Walker[1,1] Jameson and more lately by Sweeney on the effect of drugs and chemicals on *Balantidium coli* from guinea pigs and monkeys served to show that substances effective in vitro may prove inefficient in vivo Jameson found ipecac in a dilution of 1 50 000 and emetine in a dilution of 1 10 000 to be very toxic for balantidia in vitro while the arsenicals were only toxic in concentrated solutions of 1 000 Sweeney however found that in vivo emetine and ipecac were toxic to balantidia only when toxic to the host (guinea pig) as well cure was effected in only o per cent On the other hand the arsenicals stovarsol tryparsamide and parosan were highly balantidicidal and with least toxicity to the host

These experiments are interesting not only because they demonstrate how useless experiments in vitro on the therapeutic action of chemicals may be as compared to their effect in vivo but they also show that even the effect in vivo in animals may not be the same necessarily as that in man For instance ipecac and emetine were inefficient when used to eradicate the balantidia of guinea pigs except in toxic doses yet there have been undoubted cures in man by means of these drugs (Vedel and Baumel Qvarnstrom and Brandt) One gram of ipecac given daily or 0 10 gm of emetine hydrochloride given daily from five days to two weeks eradicated the parasites

The experience of a number of physicians in treating infections of Balantidium in man with arsenicals coincides with the results Sweeney obtained in guinea pigs Dutcher Marchoux Ford and Aguilar reported the cure of persons harboring *Balantidium coli* by the use of neoarsphenamine alone or with stovarsol The dosage of stovarsol varied from 1 to 3 tablets daily for three or four days It may be of advantage however to employ treparsol by the method outlined in the section on the treatment of Giardia infections in order to avoid the danger of toxicity

Mason and Cort reported the successful treatment of balantidic colitis with enemas of olive oil containing oil of chenopodium From 2 to 3 c c of oil of chenopodium to 30 c c (1 ounce) of olive oil was used Mason used 15 c c (½ ounce) of olive oil repeating the enema on the third and sixth days and Cort used 150 c c (5 ounces) of the olive oil The patient was advised to try to hold the enema for two hours unless dizziness nausea and weakness occurred A soap suds enema was given after the evacuation of the mixture of olive oil and chenopodium Cort cured twelve patients by this method

doses of neoarsphenamine at weekly intervals, and (4) frequent colonic irrigation with 1 2000 solution of thymol or quinine

This treatment was not successful always in eradicating all the protozoan infections At sight it seems very drastic and would certainly be too strenuous and weakening for debilitated subjects It would be more efficient in amoebic than in flagellate infections Yatren, a quinine derivative used for amoebic infections, has been tried with but indifferent results

Methylene blue frequently has been reported as a specific remedy for trichomonad infections (Castellani, Paranhos, and McNeil), but has been found without effect by Wenyon and O Connor, Dobell and O Connor, and others

Thymol given by mouth and by colonic lavage has been advocated by Musgrave and by others, but it has failed completely in the hands of the English investigators and of Barlow[4] in America

Numerous other drugs have been tried, such as salol, guaiacol, terebenthine, carbon tetrachloride, neoarsphenamine and other arsenicals with conflicting reports of their efficacy The colonic instillation of warm physiologic sodium chloride (from 45° to 47° C) is claimed by De Rivas to clear up these infections

Hegner[61], on the basis of some experimental work on the treatment of intestinal flagellate infections of rats advocated a carnivorous diet as a method of eradicating these infections One patient with Trichomonas infection and two patients with Giardia infection were treated with a diet high in meat, the treatment of a patient infected with Trichomonas apparently was successful, but the results were questionable in the two cases in which Giardia was harbored

Tsuchiya who investigated this mode of treatment for trichomonad infections found that diet had no effect on these flagellates no matter whether the diet favored fermentative flora in the colon or putrefactive flora, as would occur when a carnivorous (high meat) diet is fed He did not find that the by products of putrefaction, such as indols skatol, hydrogen sulphide and ammonia, in his cases were unfavorable to the existence of trichomonads as Hegner stated It must be concluded therefore that dietary measures cannot be looked to as a form of treatment of intestinal flagellate infections

It is unfortunate that at present there are no specific means of treatment for any of the flagellate infections Physicians have not found any of the drugs employed either efficacious or dependable Any treatment now used must be employed with much optimism and one should not be too enthusiastic, because the stools should be examined for several months afterward before another "cured" case is announced

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CHAPTER XLIII

UNUSUAL DISEASES AND SYMPTOM-COMPLEXES NOT DISCUSSED IN OTHER CHAPTERS *

By FREDERICK R. TAYLOR

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INTRODUCTION

In this chapter will be gathered for description a number of unusual or even rare manifestation of disease ordinarily spoken of as diseases or symptom complexes From time to time new ones will be added so that eventually the list will be reasonably complete Only a loose leaf system permitting, as it does the writing of the chapter on a serial plan could make it seem even remotely possible to try to deal with such a variety of subjects Rare diseases are like Barnum's suckers there's one born every minute to use a little hyperbole For this

* In preparing this chapter the author is grateful to many members of the Duke University Medical Faculty for suggestions especially to Dr R J Reeves Chief Roentgenologist for valuable roentgenograms to Professor Frederic M Hanes for access to the full resources of the Duke Medical Library and to Miss Judith Farrar the Medical Librarian and her staff of assistants for their unceasing courtesy and invaluable aid in the utilization of those resources

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Feb 28 1931

Etiology —This is unknown No special predisposing factor is generally recognized except heredity A considerable proportion of the earlier cases reported were in children but the condition has been described in patients whose age varied from three to seventy five years It is probable that many if not most cases begin in childhood though symptoms may not appear until adult life A sufficient number of cases have been reported in which the incidence was familial for this to appear significant though isolated cases have been described also In a few cases the parents were consanguineous Though pathologic fracture often has called attention to the disease there is no convincing evidence that trauma plays any part in etiology When symptoms occur exercise of the parts involved or anxiety states may increase the discomfort A few French writers suspect the condition to be syphilitic but most authorities disagree with this view A common etiology possibly endocrine of scleroderma osteosclerosis and universal calcinosis in children is suggested by von Bernuth[6]

Pathology —The essential feature is an increase in the density of the bones involved A single bone may be affected and the process remain localized but this is unusual More often th disease spreads from its original point or points of origin until an extensive condition results Often arising in a single focus in an extremity the process may ' flow in a longitudinal manner until the bones of the whole limb are involved At other times the disease arises in multiple foci and produces patchy areas of increased density in any or all parts of the skeleton There may be marked enlargement of the affected bones with consequent deformity and crippling but this is not a constant feature of the disease The intensely eburnated cortex tends to encroach upon the marrow cavity until it may be entirely obliterated This eburnated bone is extremely hard and brittle hence the term marble bones Fractures of the long bones especially the femur may occur from slight violence and tend to follow a transverse line without splintering resembling a transverse break in a chalk crayon Pirie[7] considers this appearance distinctive of osteosclerosis Histologically both osteoblasts and osteoclasts have been found increased in number but bone formation is obviously in excess of bone destruction Where any marrow cavity in an affected part remains unencroached upon by the thickened cortex the marrow is replaced by fibrous tissue Hence in extensive cases an associated secondary anemia of moderate degree usually is present and other blood disturbances have been described The blood chemistry including calcium and phosphorus has been found normal

A number of complications or associated conditions have been reported among them being the following aleukemic myelosis (twenty four cases collected from the literature and a twenty fifth reported by Stephens and Bredeck) [8] dermatofibrosis lenticularis disseminata[9] lymphatic pseudo leukemia ending

and other practical reasons, no effort is made at this time to group the subjects discussed in any systematic classification, desirable as that might be from a theoretical standpoint Developmental anomalies are so many and varied that merely cataloguing them all would require almost a volume and a lifetime, so only certain conditions in this group that seem of interest to the internist will be considered As with an anthology there will be many differences of opinion as to what should be included or excluded, but the loose leaf system gives opportunities to overcome the more glaring faults as they become evident Some conditions are discussed with which the author has no personal experience, because their rarity makes them of too little importance to give them enough space in Oxford Medicine to warrant a separate author, personally familiar with the condition With each description will appear a short bibliography enabling the reader to extend his study of the condition, if he so desires

Osteosclerosis

Synonyms — Marble bones, ivory bones osteosclerosis fragilis osteosclerotic anemia, osteopetrosis, osteopœcilia, melorheostosis, flowing hyperostosis osteo poikilosis, spotted bones osteopathia condensans disseminata, marmorization of bones Albers Schonberg disease

Definition — Osteosclerosis is a disease of unknown etiology affecting the skeletal system characterized by an increase in density of the bones involved, or of portions of them with a tendency to enlargement and deformity thereof marked increase in hardness and brittleness (eburnation) and a liability to pathological fracture A single bone, the bones of an entire extremity, or virtually the whole skeleton may be affected The process may be continuous from a single point of origin or may be patchy and show multiple foci

History — In 1904 Albers Schonberg[1] reported the roentgenologic appearance of the bones in this disease to the Hamburg Aertzliche Verein In 1907 Schmidt discussed congenital osteosclerosis before the Deutsche Pathologische Gesellschaft The disease appears to have been unrecognized outside of Germany before 192 and descriptions of it were largely from roentgenologic and pathologic standpoints In that year however cases were reported in considerable clinical detail by Leri and Joanny[3] in France and by Ghormley[4] in the United States The latter is the first case report in English that the writer has discovered it was worked up thoroughly from a laboratory standpoint as well as clinically and roentgenologically Recently reports of cases have been increasingly numerous especially in the last six years Moore and DeLorimier[5] have published an especially full discussion with a review of the literature of the subject



Fig 2 — Marble bone disease of skull and cervical vertebrae Note varying density in different places (From same patient as Fig 1)

in acute lymphatic leukemia achondroplasia and vitiligo [1] scleroderma and universal calcinosis[8] hydrocephalus with optic atrophy and blindness[12] necrosis of the jaw and syphilis found by several French writers to coexist in some cases

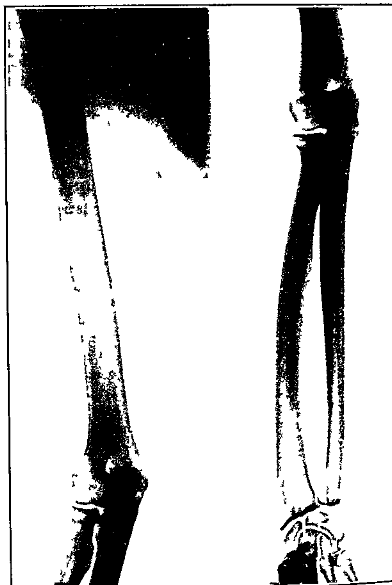


Fig 1 — Marble bone disease partially involving bones of arm Note varying density at different levels from almost normal cancellous bone to greatly thickened dense cortex to almost structureless density (Courtesy of Dr J C Aub and the X ray Department of the Peter Bent Brigham Hospital Boston)



Fig 2 — Marble bone disease of skull and cervical vertebrae Note varying density in different places (From same patient as Fig 1)

in acute lymphatic leukemia [10] achondroplasia and vitiligo[11], scleroderma and universal calcinosis[6] hydrocephalus with optic atrophy and blindness [2] necrosis of the jaw[1] and syphilis found by several French writers to coexist in some cases

Symptomatology — Often there are no symptoms of the disease per se and it is discovered accidentally in a roentgenologic examination made for a fracture or some other reason It is probable that in the vast majority of cases no symptoms exist in the early stages Many patients, however, complain of intermittent pains in the parts involved, or in the region of distribution of nerves traversing such parts These may be mild or severe and at times even lancinating In other cases the patient seeks relief because of enlargement of some part of an extremity, such as a finger shoulder, knee, etc, with consequent loss of function due to



Fig 3 — Marble bone disease advanced only small areas exist in the os calcis and 5th metatarsal and phalanx in which marmorization is not complete (Courtesy of Dr R. J Reeves Duke University Hospital from a case in Massachusetts General Hospital Boston)

deformity or swelling rather than pain The general health appears to be quite undisturbed except for the effects of pain and anxiety on the nervous system and the moderate anemia in extensive cases

Diagnosis — This is purely roentgenologic the appearance of a well-developed area of involvement being characteristic (Figs 1 2, 3 and 4) The extraordinary increase in density of the shadows of the affected bones and the thickening of the cortex with decrease or obliteration of the marrow cavity in the long bones without evidence of other disease such as chronic osteomyelitis leave little room for doubt as to the diagnosis When the process is complete in all the bony structures showing in a given film one is tempted to wonder if the film were not underexposed so dense and structureless do the bones appear, being virtual silhouettes (Fig 4) Almost always however if extensive roentgenologic studies are made, areas of normal bone will be found that contrast sharply with the extreme

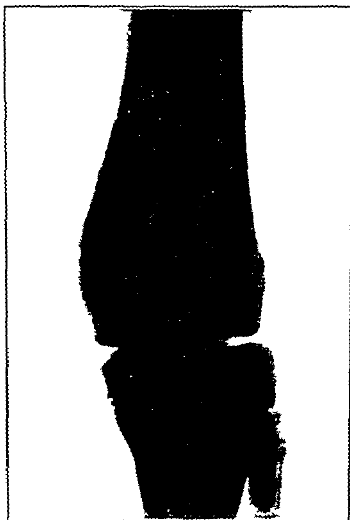


Fig 4 — Marble bone disease advanced with complete marmorization of lower femur and upper tibia with nearly complete involvement of upper fibula Note structureless silhouette like appearance of the bones (From same patient as Fig 3)

density of the abnormal areas (Figs 1 and 2) Cases of areas of increased density of bone due to carcinoma, usually metastatic, occur often, but the other features of the disease clear up the diagnosis When thickening and deformity of bone occurs, roentgenologic aid naturally will be sought, as well as in fractures Intermittent pains over a considerable period not otherwise explained, or an obscure secondary anemia, suggest a roentgenologic study of the bones to establish or exclude the presence of osteosclerosis The localized sclerosis found in Garre s type of non suppurative osteomyelitis may be confused with the early stage of osteosclerosis but in the former condition pain is more constant and trauma is usually a factor

Prognosis — According to Pounders[1] the disease may cause death in utero or very early in life Most cases, however, are exceedingly chronic and do not appear to be fatal per se As stated above, pathological fractures may occur where there is extensive involvement of the long bones The anemia does not appear to progress to a dangerous degree The skeletal involvement tends to progress very slowly throughout life, though the rate of progress varies in different cases, and complete arrest may occur Where serious complications, such as leukemia, exist the prognosis is that of the complication When death is not due to such complication, it usually results from some intercurrent condition or senile changes

Treatment — With our present knowledge, no treatment affects the progress of the disease per se nor have we any effective prophylaxis Ochsner and Moser[13] report a case involving the 6th cervical vertebra in a 75 year old woman who complained of severe pain in the left forearm and three fingers for two months in which complete relief from pain was obtained by roentgenologic treatment When anemia exists iron is indicated Fractures will require appropriate surgical treatment and deformities may indicate orthopedic aid Oral hygiene may lessen the danger of necrosis of the jaw Drugs promoting the calcification of bone such as calcium, phosphorus cod liver oil viosterol etc should be avoided as should excessive ultraviolet radiation Childbearing is contraindicated

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ARACHNODACTYLY

Synonyms — Spider hand dolichostenomelia

Definition — A congenital peculiarity of the extremities most marked in the distal portions characterized by elongation and thinning of the bones

History — In 1896 A B Marfan reported a case of this condition in a five and one half year old girl to the Societe medicale des Hopitaux de Paris[1] According to Brailsford Archard originated the term arachnodactyly in 1902 Many cases have been reported in recent years

Etiology — This is unknown Endocrine disorders especially pituitary have been suggested but remain unproved

Pathology — This consists essentially of a notable lengthening of the bones of the extremities especially the metacarpals metatarsals and the phalanges of both the hands and feet There is also a certain amount of thinning of the bones involved Other slight deformities of the extremities have been described In Marfan s original case the fingers showed slight enlargement of the lower ends of the first phalanges and upper ends of the second the second being deflected somewhat towards the radial side The fingers but not the thumbs were flexed and could not be fully extended because of fibrous contractures of the tendons which limited the movements of the interphalangeal joints

Symptomatology — There are no subjective symptoms other than the consciousness of the deformity and some limitation of motion as noted above. If there be sufficient deformity of the feet, the child may not learn to walk at the normal time. Marfan's patient had never walked. The striking elongation of the hands and feet is diagnostic. While all the metacarpals, metatarsals and phalanges are of great length, there may be disproportionate elongation. Marfan's patient showed the metacarpals long in proportion to the phalanges and the ring fingers longer than the middle fingers. The elongation and thinning of the digits gives rise to the name "spider hand", a poor term, however, as the feet are also markedly affected. Deflection of the fingers towards the radial side and contractures may be noted, as described under Pathology. Not only the hands and feet, but to a somewhat lesser degree the forearms and legs, and in slight measure the arms and thighs are longer and thinner than normal. There is no true atrophy of the muscles, and the electrical reactions are normal. In Marfan's patient the wrist and shoulder movements were free, the elbows slightly limited by fibrous contractures. Despite her deformity, she could use her hands to feed herself, dress her doll, etc. Her feet were deformed, as were her hands, being not only extremely long, but with elongated toes tending to cross one another, due to lateral deflection. The legs also were very long, the thighs being similarly affected, but to a lesser degree. The toes, feet and ankles moved freely, but knee action was limited by fibrous contractures of the joints, and this was the cause of her failure to learn to walk. Co-ordination was good and there was no involvement of the nervous system.

A very large number of associated defects have been noted. Cockayne states that of all developmental anomalies arachnodactyly is peculiarly liable to have other defects combined with it. Many of these involve the eyes, usually bilaterally, especially dislocation of the lens. Among the associated abnormalities outside the eye there have been reported anomalies of the skull, subcutaneous fat, hands and feet, congenital heart disease, multiple small cysts of anterior pituitary, various types of spinal curvature, a thin, witch-like appearance, a senile stare, cyclic vomiting, bilateral congenital dislocation of hips, winged scapulae, imbecility, atrophy of ribs on one side, beaded ribs, spina bifida, various exostoses, bunions, etc.

Marfan's *syndrome*, a term sometimes used for arachnodactyly, should not be confused with so called Marfan's disease, a name at times given to a type of spastic paraplegia due to heredosyphilis.

Diagnosis and Treatment — Diagnosis can be made from observing the deformities already described. Treatment should be directed toward special training in the use of deformed structures. An orthopedist should be consulted. Other specialists can help in accordance with the various special anomalies.

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ARTHROGRYPOSIS MULTIPLEX CONGENITA

Definition —Stern defines this as a congenital limitation of motion in all the joints of the body except maxillary and vertebral a characteristic rotation deformity of the arms inward and of the thighs outward and a fusiform or cylindric shape to the elbows and knees the latter of which are extended while the wrists are flexed the hands compressed and the feet twisted[1] There are however variations from this picture as vertebral involvement has been described and the condition may be limited to a single extremity The head and neck are normal Arthrogryposis means curved joint

History —So far as the writer knows Stern s paper in 1923 was the first description of this disease as a distinct clinical entity

Etiology —This is unknown but Stern suggests that the condition may be due to a rare combination of intrauterine periarthritis and pressure in forced po itions It has been found in both whites and negroes

Pathology —The bony portions of the joints are normal The essential trouble seems to be a thickening of the joint capsules Motion is free within narrow limits but beyond these limits both active and passive motion is impossible Muscle spasm and contracture are absent General muscular development is poor but true atrophy does not occur Stern s patients children seemed somewhat backward mentally Other complications or associated conditions that have been found occasionally are congenital luxation or subluxation of one or two joints and congenital absence of various muscles

Symptoms and Physical Signs —These are sufficiently described in the definition and in discussing the pathology Sensory symptoms appear to be absent

Diagnosis —This rests on the appearance of the patient described above plus a normal roentgenologic bony picture No other condition known to the writer resembles it closely enough to be confusing

Treatment —Many forms of treatment have been tried including operative

methods, but without benefit Many children can be trained to do some useful work with their hands, but those with severe cases cannot make a living as a rule, and where there is no other means of support, institutional care is indicated in order that they may be trained to maximum efficiency and have work brought to them, so they may occupy their time and contribute some towards their support

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MORQUIO S DISEASE

Definition —A peculiar form of familial dwarfism characterized by an osseous dystrophy producing symmetrical deformities, notably a marked shortening and widening of the thorax, epiphyseal changes and often atrophy of the head of the femora

History —Morquio of Montevideo reported the condition in 1929 as affecting four out of five children in one family[1]

Etiology —This is unknown

Pathology and Symptomatology —These will be considered together, as much of the pathology is best observed from the physical appearance of the subjects of the disease, and much of it is exhibited in a roentgenologic study Morquio s children appeared healthy at birth, and bony changes were not noted until they began to walk Then widespread changes occurred, 'sparing only the head and face and causing no pain or other suffering but functional troubles affecting especially motility and destroying the harmony of the body (quoted by Davis and Currier) The deformities were symmetrical The extremities were of normal length, though deformed, and the thorax markedly shortened and widened Roentgenograms showed bony proliferation in many parts of the skeleton, including the spine, shoulders, knees and epiphyses of the elbows on the other hand, there was absence of ossification in certain parts, notably the wrists Morquio and some others failed to find any involvement of the head, but some writers have described a large head with diastasis of some of the sutures and fusion of others with eventual optic atrophy and consequent blindness Davis and Currier made an encephalogram on one patient which showed symmetrical enlargement of the lateral ventricles, slight enlargement of the third ventricle and a patchy distribution of air over the cortex Kyphosis occurs and in a number of cases considerable destruction of the acetabula with

atrophy of the heads of the femora has been noted. Genu valgum is a part of the *picture and the knees show some bony proliferation with roughening* of the joint surfaces The bones of the forearm are bowed, and ossification is retarded in the wrists The general physical appearance is that of "a dwarfed child with eyes widely separated, nose depressed, neck short sternum pushed and bent forward like a shelf on which the chin rests spine kyphotic hips

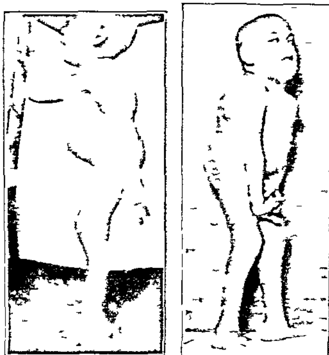


FIG. —One of patients described by Morquio in Arch. di Med. des Enfants 1929, XXXII 1 9. (Courtesy of the American Journal of Diseases of Children.)

flexed so that the child appears to crouch with hands extending almost to the markedly knocked knees feet kept apart and the ends of the long bones prominent. There is marked generalized epiphyseal disturbance and abnormal cartilage growth" (quoted from Barnett) Potbelly is the rule as in many forms of dwarfism. Histologically the bone is normal. The urine blood count and Kahn test for syphilis have been found normal Morquio found a low blood calcium, but other observers report the blood calcium, phosphorus and sugar

normal and have found a normal glucose tolerance Meyer and Brennemann have given an interesting illustrated account of the disease[4]

Diagnosis is made by inspection, the deformities being characteristic

Prognosis — Once the changes are fully established, they are permanent

Treatment — There is no curative treatment Various orthopedic measures, such as osteotomy[3], may be attempted to lessen functional disability

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ADIPOSIS DOLOROSA

Synonyms — Dercum s syndrome Dercum's disease

Definition — Adiposis dolorosa is a disturbance of fat metabolism characterized by the deposit of localized masses of fat, most of which are both painful and tender

History — F X Dercum made his first report of this condition in a patient in the Philadelphia Hospital before the American Neurological Association in Washington in September, 1888, under the title "A Subcutaneous Connective Tissue Dystrophy of the Arms and Back With Symptoms Resembling Myxedema' This was published in the University (of Pennsylvania) Medical Magazine for December of the same year About two years later a second case, also from the Philadelphia Hospital was reported to the Philadelphia Neurological Society by Dr Frederick Henry under the name of myxedematoid dystrophy and published in the Journal of Nervous and Mental Diseases for March, 1891 In November, 1892 Dercum reported another case and compared it with the first two cases showing that though the three differed in details, they appeared to be examples of a single clinical entity for which he proposed the name by which the condition is now generally known, *adiposis dolorosa* because th two most prominent clinical features of the condition are fatty swellings and pain[1]

Etiology and Pathology — Though a distinct clinical entity, adiposis dolorosa is probably not a definite pathological one, and despite many champions

of one theory or another probably has no single etiology Some have claimed that it is a pituitary disorder only to find cases showing no evidence of hypophyseal disease Others have ascribed a thyro-ovarian origin with as little constancy of findings Still others favor some hypothalamic disturbance (cf Putnam Diseases of the Hypophysis Vol III Chap XIV) Foot Good and Menard, after an exhaustive study conclude that the cause is a variable poly glandular disturbance and that about all that can be said with confidence is that we are dealing with a clinical picture which occurs in certain cases in which fat metabolism is disturbed in one way or another From the viewpoint of functional pathology and biochemistry there is as much variability as from that of patho logical anatomy[3] Increased sugar tolerance with epileptiform convulsions has been described[4] but glycosuria has also been found Adiposis dolorosa involving the lower half of the body following epidemic encephalomyelitis has been re ported[6] as has symmetrical facial atrophy with segmentary adiposis dolorosa[7] These however are individual cases the peculiar features of which are not essen tial parts of the general clinical picture

Symptomatology —While the details of different cases will vary Dercum s original discussion of the findings in the first three cases on record gives such a graphic picture that it seems worth while to present the essentials of that discussion here for both its clinical and historical value

The first case was that of a 51 year old Irish domestic with a normal men strual history At the age of 48 or 49 she noticed that her upper arms had swollen until they were very large There were no other symptoms for a year after that Then she began to suffer sharp darting pains in her right arm in creasing in severity and extent and finally involving the shoulder neck and forearm At times she felt as if hot water were being poured on her arm at others as if her fingers were being torn apart She was never free from these pains but had exacerbations of great severity lasting hours or days Physical examination showed enormous enlargement of the back shoulders upper arms and sides of the chest huge pendulous masses were in the arms and back These were elastic firm and non pitting In places they felt as if finely lobulated in others like bunches of worms under the skin The skin itself was not thickened Motion of the right arm was very painful and the head wa fixed to avoid the pain of moving it The right arm was very tender to pressure throughout the swollen areas and the nerve trunks passing through them were exquisitively sensitive The left arm was not painful despite huge swellings The muscles were not involved in the swellings for the masses were uninfluenced by contracting them They were obviously beneath the swellings However the affected parts were very weak especially the right hand The muscles of the shoulders and arms gave negative electrical reactions partly at least due to

the resistance of intervening tissue Those of the foreams gave slight quantitative and qualitative changes There was a distinct reaction of degeneration in the thenar and hypothenar muscles, especially in the right hand Skin sensation was much decreased, especially on the right Sensation was impaired in the right lower extremity but was normal in the left No other part of the body was involved Seven months later marked lobulation of the swollen tissue was noted with hard cake like masses, which were more noticeable during paroxysms of pain There was some improvement in the pain the following summer, though occasional pains now appeared in the left arm DeSchweinitz found contraction of the visual fields for form and color Additional notes state that in the past few years the patient had vomited blood several times She had cardiac dyspnea in the late stages with a pulse rate of 95 to 110 Shooting pains and an extensive deposit of tissue developed in the abdomen A biopsy showed only embryonal connective tissue and fat with occasional inclusions of nerve elements which were denser than normal and rich in nuclei

The second case (Henry s) was in a 64 year old Englishman His trouble had started at the age of 49 when in California He noted that he was constantly cold about the knees and soon noted swellings there There was a localized mass on the inner aspect of each knee with dull aching pain there and less perspiration than normal Ten years after onset he developed an epigastric swelling which spread until nearly the whole abdominal wall was involved From his knees the process spread to the outer thighs and hips where large masses developed Later the left buttock became affected His general appearance was that of a very obese man, but the fat was unevenly distributed He died of congestive heart failure Necropsy specimens obtained for microscopic study were thrown away by mistake

The third case was in a 60 year old German widow Many years previously a lump had appeared on the back of he neck Since then many swellings had developed in various places The menopause had occurred at 46 Before that she had had menorrhagia at times and had also had hematemesis and epistaxis For the past two years some mental impairment had been noticed There were soft, fatty masses in the arms, abdomen, mons veneris, back of neck and hips There were none in the forearms hands, face, thighs or buttocks The masses were nodular and tender The urine showed albumin but no casts The patient was extremely weak No ocular abnormalities were found, but the patient was too weak for a detailed study of the visual fields She died in coma The necropsy specimens from this patient were lost too!

From the above notes it may be seen that the essential clinical picture consists of localized masses of fat which may become grotesquely large and which usually are both painful and tender throughout, especially along the

course of the underlying nerves Hemorrhages from the stomach and elsewhere may occur

Diagnosis —In a typical case the diagnosis is obvious In the early stages if pain is absent it may be indistinguishable from lipomatosis but the appearance of the characteristic pain and tenderness will establish the nature of the condition The irregular distribution of the fat in lumpy masses will differentiate from simple obesity even when pain is absent

Prognosis —The di ease is chronic progressive and of indefinite duration Death usually results from myocardial failure or from some intercurrent condition

Treatment —This is of necessity empirical and symptomatic Until we have more evidence of some definite etiology in a given case endocrine therapy will of necessity be purely experimental yet judicious experimentation with thyroid preparations and perhaps certain other endocrines may be permissible in such a distressing condition Physical therapy may be useful to relieve pain and should be tried as analgesic drugs should be avoided as far as practicable in such a chronic condition Of physical measures radiant heat diathermy and possibly roentgen therapy would seem the most reasonable, but they should be given by an expert especially the last two

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decrease of food intake during attacks due to inability to swallow as the chief cause of this metabolic peculiarity

Mr Marvin Herrington a medical student at Duke University has authorized the writer to state that in his case creatin is constantly present in the urine, varying from 0 1 5 gm to 0 75 gm per 24 hrs without obvious relation to his attacks

These and similar findings have led many observers to consider periodic paralysis as a disease involving the muscles essentially rather than the nervous system Creatinine being non toxic simple retention is not the cause of the disease

Symptomatology —The onset of the first attack usually is in childhood or adolescence though first attacks have been reported in infancy and as late as 36 years old In the records of one family attacks began at puberty in all who were affected A typical severe attack may be described as follows Occasionally there may be prodromal symptoms of fatigue in the muscles to be involved for a day or so before the actual paralysis Very rarely dull aching has been reported but much more often there are no sensory symptoms at all The onset of the paralysis is gradual It usually comes on late at night after some hours in bed especially if unusual exercise has been indulged in the day previously It may come on in the daytime if the patient has been kept in bed The lower extremities usually are affected first in their proximal mu cles After the thighs legs and feet are involved the arms forearms and hands become affected and last the trunk and neck muscles Power returns gradually in reverse order as the attack passes off In very severe attacks the sphincters may be affected Occasionally the patient may improve and relapse before wholly recovering from an attack The legs alone or the legs and one or both arms may be involved Abortive attacks showing only slight weakness have been described Individual attacks in the same patient may vary in duration extent severity and frequency It is said that there may be no desire to void urine or feces yet true retention does not occur At the height of a severe attack there is a widespread flaccid paralysis of almost all the muscles of the body though the muscles supplied by the cranial nerves often escape The patient is perfectly conscious but lies utterly helpless in bed unable to turn his head or move a finger The muscular reflexes and electrical excitability are lost or in a milder attack diminished They return with recovery from the attack The diaphragm rarely is involved but the intercostals are as a rule and this makes respiration shallow Some cardiac dilatation has been noted by a number of observers in severe attacks disappearing with a disappearance of the paralysis Swallowing often is difficult because of the muscular weakness Fever is absent Sensory symptoms are conspicuous by their absence though rarely some numbness and tingling has been complained of Intervals between attacks

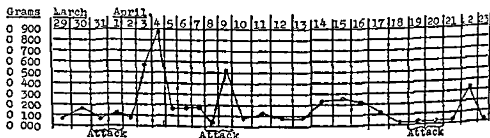
Family Periodic Paralysis

Definition — A rare familial disease characterized by transient attacks of flaccid paralysis with loss or in mild attacks, decrease of tendon reflexes and of electrical and mechanical excitability of muscles

History — According to E W Taylor[1], Hartwig described a typical case in 1874 in his inaugural dissertation at Halle Prior to this, Taylor states that Cavare and Romberg described less typical cases, both said to have been malarial in origin and relieved by quinine, so he considers them questionable examples of periodic paralysis Taylor's paper, published in 1898, collected twenty cases of the disease which he considered authentic A number of reports have appeared since then, but the disease still is distinctly rare

Etiology and Pathology — Though there have been many speculations regarding the essential underlying processes of this strange disease, they are as yet unknown Heredity is definitely recognized as a predisposing factor Atwood states that nineteen cases have been traced in one family line The sexes are affected about equally Some patients have had attacks alternating with migraine Buzzard suggests an insufficiency of the lymph circulation as

CREATININE EXCRETION — PERIODIC PARALYSIS
(Modified from Mitchell Flexner and Edsall)



the exciting cause of the attacks Holtzapple[4] suggests vasomotor spasm, but the gradual orderly development of the paralysis and its equally gradual and orderly disappearance would seem to argue against this as a very important factor Blood serum taken from patients during an attack has caused no significant effects when injected into rabbits Mitchell, Flexner and Edsall[5] have noted a marked disturbance of creatinine metabolism They found a very low creatinine output in the urine before every attack, often lasting into, through and even occasionally for a brief period after the attack, with a sharp rise above normal succeeding the fall The low values before the attacks exclude

decrease of food intake during attacks due to inability to swallow as the *chief cause of this metabolic peculiarity*

Mr Marvin Herrington a medical student at Duke University has authorized the writer to state that in his case creatin is constantly present in the urine varying from 0 1 5 gm to 0 75 gm per 24 hrs without obvious relation to his attacks

These and similar findings have led many observers to consider periodic paralysis as a *disease involving the muscles essentially rather than the nervous system* Creatinine being non toxic simple retention is not the cause of the disease

Symptomatology —The onset of the first attack usually is in childhood or adolescence though first attacks have been reported in infancy and as late as 36 years old In the records of one family attacks began at puberty in all who were affected A typical severe attack may be described as follows Occasionally there may be prodromal symptoms of fatigue in the muscles to be involved for a day or so before the actual paralysis Very rarely dull aching has been reported but much more often there are no sensory symptoms at all The onset of the paralysis is gradual It usually comes on late at night after some hours in bed especially if unusual exercise has been indulged in the day previously It may come on in the daytime if the patient has been kept in bed The lower extremities usually are affected first in their proximal muscles After the thighs legs and feet are involved the arms forearms and hands become affected and last the trunk and neck muscles Power returns gradually in reverse order as the attack passes off In very severe attacks the sphincters may be affected Occasionally the patient may improve and relapse before wholly recovering from an attack The legs alone or the legs and one or both arms may be involved Abortive attacks showing only slight weakness have been described Individual attacks in the same *patient may vary in duration extent severity and frequency* It is said that there may be no desire to void urine or feces yet true retention does not occur At the height of a severe attack there is a widespread flaccid paralysis of almost all the muscles of the body though the muscles supplied by the cranial nerves often escape The patient is perfectly conscious but lies utterly helpless in bed unable to turn his head or move a finger The muscular reflexes and electrical excitability are lost or in a milder attack diminished They return with recovery from the attack The diaphragm rarely is involved but the intercostals are as a rule and this makes respiration shallow Some cardiac dilatation has been noted by a number of observers in severe attacks disappearing with a disappearance of the paralysis Swallowing often is difficult because of the muscular weakness Fever is absent Sensory symptoms are conspicuous by their absence though rarely some numbness and tingling has been complained of Intervals between attacks

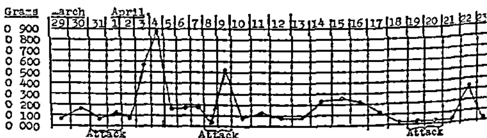
Family Periodic Paralysis

Definition — A rare familial disease characterized by transient attacks of flaccid paralysis with loss or, in mild attacks, decrease of tendon reflexes and of electrical and mechanical excitability of muscles

History — According to E W Taylor[1], Hartwig described a typical case in 1874 in his inaugural dissertation at Halle Prior to this, Taylor states that Cavare and Romberg described less typical cases, both said to have been malarial in origin and relieved by quinine, so he considers them questionable examples of periodic paralysis Taylor's paper, published in 1898 collected twenty cases of the disease which he considered authentic A number of reports have appeared since then but the disease still is distinctly rare

Etiology and Pathology — Though there have been many speculations regarding the essential underlying processes of this strange disease, they are as yet unknown Heredity is definitely recognized as a predisposing factor Atwood states that nineteen cases have been traced in one family line The sexes are affected about equally Some patients have had attacks alternating with migraine Buzzard suggests an insufficiency of the lymph circulation as

CREATININE EXCRETION — PERIODIC PARALYSIS
(Modified from Mitchell Flexner and Edsall)



the exciting cause of the attacks Holtzapple[4] suggests vasomotor spasm but the gradual orderly development of the paralysis and its equally gradual and orderly disappearance would seem to argue against this as a very important factor Blood serum taken from patients during an attack has caused no significant effects when injected into rabbits Mitchell, Flexner and Edsall[5] have noted a marked disturbance of creatinine metabolism They found a very low creatinine output in the urine before every attack often lasting into through and even occasionally for a brief period after the attack, with a sharp rise above normal succeeding the fall The low values before the attacks exclude

Barcoo Sickness*

Synonyms — Barcoo spew Bellyander spew

Definition — A non febrile disease of sudden onset characterized by vomiting without loss of appetite by marked fatigue and weakness and at times by rapid emaciation which yields promptly to quinine therapy Barcoo *sickness* must be distinguished from Barcoo *rot* a term used in parts of Australia for a type of ulcerating pyodermia that occurs in various parts of the world under several different names

Distribution — Barcoo sickness is said to be confined to a small territory in the Barcoo River Cooper s Creek district and along parts of the Diamantina River in South Australia though it resembles the Grass Sickness of Western Australia and Queensland so closely that the two diseases may well be considered identical

Etiology — This is unknown but certain factors suggest that it may be an acute infection possibly of protozoan origin It occurs along the streams mentioned in the rainy season and disappears with the coming of dry weather The prompt response to quinine has led some observers to postulate a malarial origin but the writer knows of no blood studies to support this and the total lack of fever throughout the disease would seem to argue strongly against that supposition Many inhabitants of the affected areas suspect a connection between the swarms of flies that occur in those areas in times of heavy rainfall and outbreaks of the disease

Symptomatology — According to Bickle[1] the onset is very sudden A man may start a meal with a good appetite and get a sudden attack of vomiting Once his stomach is emptied he may return to the table with his appetite unimpaired eat more food and retain it Others may have two or more attacks of vomiting in succession but keep returning to the table with a keen appetite until able to retain what they eat Still others can retain no food and rapidly become emaciated A feeling of profound fatigue and weakness is the rule Fever is absent and no symptoms or signs other than those above mentioned have been described so far as the writer knows

Diagnosis — The above picture coming on in the rainy season in localities where the disease is known to occur should offer no difficulty in diagnosis

Prognosis — This should be invariably good as treatment appears to be uniformly effective

Treatment — Quinine appears to have a specific action Apparently a few

* In preparing this section the author is indebted to the W F Prior Co of Hagerstown Maryland for photostatic and other copies of original Australian papers

vary from a few hours to a few years A single attack without recurrence has been reported The muscles do not atrophy

Diagnosis — Immediate diagnosis may be difficult or impossible when the patient is seen in his first attack and no family history of the disease is obtainable The absence of muscular reflexes and of electrical excitability argues against hysteria, as does the absence of fever against poliomyelitis In a typical case with a history of previous attacks and a family history of the disease there should be no difficulty in diagnosis, as the fully developed clinical picture is unique

Prognosis — This in general is good Rarely death has occurred in an attack, apparently from cardiac weakness, and it is possible for accidental factors to be fatal in the patient s helpless condition, as, e g , strangling on food etc Failure of the respiratory muscles to a fatal degree is very unusual, if it ever occurs As a rule the attacks tend to decrease in duration and frequency as the patient gets older and often cease entirely about the time of the climacteric

Treatment — No drug has thus far been reported as dependably effective Glycine and ephedrine have been tried and apparently found wanting During an attack the patient should not be left alone, and his throat must be kept clear of regurgitated food etc Food should be given in mall amount only and consist of concentrated nourishing liquids The patient and his family should be reassured as to the outcome of the attack Any factors found tending to precipitate attacks in a given person, such as emotion, fatigue, undue lack of exercise etc , should be eliminated as far as possible

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Rabbit s Blood Dermatitis

Synonym — Johnson Taylor disease

Definition — A localized, acute, vesicular skin eruption apparently produced by contact with the blood of the wild cotton tail rabbit, *Sylvilagus floridanus*, under conditions imperfectly understood at this time

Introduction — The condition to be described is purely a dermatologic one so far as man is concerned Two considerations, however, move the writer to include it in the present chapter though he is quite aware that this work is not intended to cover the general field of dermatology The first one is that the unusual number of cases observed by many physicians in one particular year in at least three states of the mid southern Atlantic seaboard (Virginia and the Carolinas) contrasted with the rarity of the condition in other years, suggests the possibility that some epizootic disease of rabbits prevalent during that year may be the underlying cause of the condition The second consideration is that, so far as the writer knows the disease has not been described in any systematic medical treatise to date yet it seems of sufficient interest to warrant inclusion in some such work, in the hope that if it reappears in a considerable number of cases further work may be stimulated to clear up many obscure features of the disease as known at present

History — In 1930 the writer published the only description of the disease thus far known to him in the literature under the title, Epidemic of Dermatitis Venenata Due to a Hitherto Undescribed Cause '[1] The first case that came to his notice was in the fall of 19 9, when a man stated that he and a friend had developed an eruption on their hands the day following a rabbit hunt, after skinning and cleaning the game At the time, the writer regarded the condition as a simple dermatitis venenata of plant origin The condition cleared up promptly on treatment Early in January, 1930 a young woman appeared with a similar though less severe condition on her hands and was treated for a dermatitis venenata supposedly due to sensitiveness to the needles of a Christmas tree Recovery was prompt but soon afterwards she asked if handling rabbits could have had anything to do with the condition and added that she had dressed a wild

rabbit the day before the eruption appeared Also she had heard of two more cases in rabbit hunters This recalled the statement of the man the preceding fall and led to further investigation Although the patient appeared to be in perfect general health a specimen of her blood was sent to Dr C A Shore Director of the North Carolina State Laboratory of Hygiene with a letter describing the case He forwarded the blood to the United States Hygienic Laboratory which reported it negative for tularemia He also wrote that he had heard of a number of similar cases that season especially in the territory around Aberdeen N C that he had seen one case his diagnosis being dermatitis venenata and that in all these cases the patients had stated that the condition seemed to be associated with handling freshly killed wild rabbits Conversation with several other physicians elicited the fact that they had seen a number of similar cases that season and in every case the patient had volunteered the idea that the condition was associated with handling wild rabbits The matter was brought before the Tri State Medical Society of Virginia and the Carolinas in February 1930 and a number of the members present stated that they had seen the condition that season always attributed by the patients to handling rabbits Among the cases cited was that of a 73 year old woman who had dressed a rabbit just before the eruption had appeared and who had not been exposed to contact with any wild vegetation Dr Wingate M Johnson of Winston Salem N C was the one member present who recalled seeing the condition several years previously In one season he had two such patients One a man had killed a rabbit and stuffed it in his hip pocket The blood soaked through to his buttock and back of his thighs and the characteristic eruption appeared where the blood had come in contact with the skin The other patient a boy killed a rabbit and carried it home swinging it alongside his thigh and leg The blood ran through his trouser leg and the characteristic eruption appeared shortly after wherever the blood had touched his skin Dr Johnson reported his cases that year to the Forsyth County (N C) Medical Society but did not publish the report He deserves priority however for describing the condition several years before the present writer s publication He stated that he had never seen such a case before or since the two cases he reported and that he had not been able to find anyone else who had observed the condition at the time he made his report The other physicians with whom the writer conversed had seen such cases only the same season that the writer saw his The following season of 1930–1931 the author saw only one case and has not seen any cases since Shortly after publishing his account he received a letter from a physician in Pennsylvania whose name he does not now recall stating that he had observed similar cases that season for the first time

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Pathology and Symptomatology — Grossly the lesions appear identical with those seen in ordinary rhus poisoning They are limited however, to areas of skin coming in contact with the blood or tissue of the wild cotton tail rabbit They vary in severity as in rhus poisoning from a few discrete vesicles to a confluent eruption with marked swelling of the parts involved The local symptoms of itching and burning are practically the same as those of a similar grade of rhus poisoning No constitutional symptoms have been observed No ulceration, conjunctivitis glandular involvement, lymphangitis, fever, or anything else to suggest tularemia has been noted In a case studied rather carefully, but somewhat late, by the author a general physical examination made three weeks after the eruption had cleared up revealed nothing abnormal the urine, stool and blood film including a differential white cell count, were normal and the tularemia agglutination and Wassermann reactions were negative

Diagnosis — This depends on a history of handling rabbits just before the appearance of a vesicular eruption identical in appearance with that characteristic of rhus poisoning without other findings usually at a season when rhus poisoning is not prevalent

Treatment — The local application of simple soothing lotions is all that is ordinarily required The writer has used lotio alba in his cases Recovery usually is complete in a few days

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PERIARTERITIS NODOSA

Synonyms — Kussmaul s disease, Kussmaul Maier disease

Definition — Periarteritis nodosa is an inflammatory disease of the arteries, usually acute but occasionally subacute or even chronic, characterized by the development of multiple nodes and at times small aneurisms in the walls of the affected vessels, accompanied by a variety of local and constitutional symptoms Syphilitic nodular arteritis is excluded

History — According to Goodridge[1], Rokitansky recognized the disease and described its gross pathology in 1852 Kussmaul and Maier gave a clinico

pathologic description of a case including histologic studies in 1866 and named the disease periarteritis nodosa During life the patient was thought to have trichiniasis but necropsy showed the nature of the trouble The condition is not known as Rokitansky s disease because that name is sometimes applied to acute yellow atrophy of the liver

Etiology —This is unknown Some authorities believe that a variety of pyogenic organisms notably the various types of streptococci may be responsible for the condition According to Osler[2] tonsillitis may precede the attack The consistently negative blood cultures fail to support a pyogenic theory Others suspect a filterable virus[1] There is a syphilitic form of nodular arteritis but its pathology course prognosis and treatment are different from those of the condition under discussion A relation to rheumatic fever has been emphasized[11]

Incidence and Distribution —The disease probably is not very rare Though described in Germany in the middle of the last century the first French case to be recognized was reported in 1928 by Debre Leroux Lelong and Gauthier Villars[3] who collected 153 cases from the world s literature There seems little if any geographic limitation as cases have been reported from Germany Austria France Italy Belgium Norway the United States Brazil and Australia though most of the reports have come from Central Europe The negro may be affected the writer saw a case a negro child autopsied by Professor S F Ravenel of Greensboro N C the diagnosis being confirmed by Dr W D Forbus of Duke University to whom the organs were taken Most cases occur in early adult life but patients have been reported as young as 3½ years and as old as 6 years The sex incidence shows males predominating in a ratio of five to one[1] Bernardinelli[4] believes that alcohol may be a predisposing factor but the evidence is hardly conclusive Warfield states that a similar disease has been reported in stags

Pathology —The adventitia and media are chiefly involved and show multiple nodular areas of inflammatory infiltration often associated with minute aneurisms The nodules are yellowish white in color and vary in size from bare visibility to that of a pea Larger lesions are frequent but are aneurismal in nature Thrombosis may occur The appearance of an extensively involved vessel may suggest a string of beads of various sizes The coronary arteries and medium sized renal and gastrointestinal arteries seem especially susceptible but almost any region of the body may show widespread arterial involvement and the disease may be pretty well generalized throughout the system Muscular atrophy occurs in some cases[6]

Symptomatology —This is extremely variable depending on what arteries are chiefly affected and the degree of their involvement The onset usually s abrupt and febrile with the signs of an acute general infection such as head

about the etiology at this time The frequency of the condition in a single season, and its rarity before and since, certainly seem to suggest that some unusual epizootic had appeared among rabbits that season

Pathology and Symptomatology — Grossly, the lesions appear identical with those seen in ordinary rhus poisoning They are limited, however, to areas of skin coming in contact with the blood or tissue of the wild cotton tail rabbit They vary in severity as in rhus poisoning from a few discrete vesicles to a confluent eruption with marked swelling of the parts involved The local symptoms of itching and burning are practically the same as those of a similar grade of rhus poisoning No constitutional symptoms have been observed No ulceration conjunctivitis, glandular involvement, lymphangitis, fever, or anything else to suggest tularemia has been noted In a case studied rather carefully, but somewhat late, by the author, a general physical examination made three weeks after the eruption had cleared up revealed nothing abnormal the urine stool, and blood film including a differential white cell count were normal, and the tularemia agglutination and Wassermann reactions were negative

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History — According to Goodridge[1], Rokitansky recognized the disease and described its gross pathology in 1852 Kussmaul and Maier gave a clinico

at first, and the edges were sharp but they increased in size and became covered with a whitish membrane Cicatrization occurred in about thirty days without treatment Nodules also appeared in his neck chest and arms but neither ulcerated nor disappeared They were freely movable and non adherent to surrounding structures His calf muscles were tender on palpation His right eye showed a visual acuity of $\frac{1}{3}$ unimproved by glasses with an external rectus paralysis dilated retinal veins contracted retinal arteries and edema of the temporal part of the optic nerve His left eye was normal save for presbyopia The capillary loops in his nailbeds were sinuous and irregular Extensive laboratory studies including the Wassermann reaction were negative

Diagnosis — This depends on finding the characteristic nodules demonstrating their nature at biopsy and on the exclusion of certain other conditions The condition may be suspected when the tetrad of Meyer and Brinkman is observed[1, 11] This is chlorotic marasmus polyneuritis and polymyositis striking abdominal manifestations and nephritis A marked eosinophilia without evidence of parasitic disease would add great probability of periarteritis nodosa

Rothstein and Welt[8] state that periarteritis nodosa should be considered and subcutaneous nodules sought in every case of acute or chronic sepsis with sterile blood cultures and bizarre symptomatology unexplainable on a common basis especially if associated with severe anemia fever gastrointestinal symptoms joint muscle and skin manifestations and renal involvement with hypertension

Syphilis must be excluded by the usual laboratory procedures and in case of any doubt by a therapeutic test The resemblance to *trichiniasis* may be striking in cases showing vomiting diarrhea severe muscle pains and tenderness and edema of various parts of the body Trichinellæ are of course not found in the muscles on biopsy in periarteritis nodosa The nodules of *erythema nodosum* should cause no confusion as they are usually larger dusky red and never show the beading along the arteries sometimes found in periarteritis nodosa *Septicemia* is excluded by constantly negative blood cultures

Typhoid fever and *meningitis* may be simulated but laboratory procedures should differentiate them Occasionally abdominal symptoms may be so severe that a *ruptured viscus* or *acute pancreatitis* may be suspected and indeed cases of periarteritis nodosa have been reported in which intestinal perforation and peritonitis occurred If the characteristic nodules are not evident on inspection or palpation there may be no suspicion of the real trouble

Coronary thrombosis may occur and be recognized while the underlying trouble of which it is a complication passes unnoticed

Prognosis — While an exceptional case may run a subacute or chronic course the disease usually is fatal in from one to a few weeks Two to three

ache vertigo, chills, vomiting and muscular pains Rarely it may be insidious The physical signs vary according to the location and degree of vascular involvement Edema of various parts of the body is frequent

Debre and his associates[3] recognize five chief types of the disease as follows (1) a terminal phase of some grave infectious condition, with fever, pallor prostration and slight splenomegaly, (2) a painful syndrome with nodular masses in the muscles, especially of the lower extremities, suggesting trichiniasis (3) a cutaneous type showing a papulo vesiculo bullous eruption, in which the bullæ and vesicles are filled with blood and ecchymotic plaques appear which may ulcerate bloody ulcerated erosions may be found on the buccal and pharyngeal mucosæ (4) a digestive abdominal type with anorexia, vomiting abdominal pain meteorism and mucosanguinolent stools, (5) a renal type with hematuria or simulating an acute surgical condition[10]

To these we might add two rarer types, viz (6) a cerebral type with a great variety of cerebral vascular symptoms such as headache, excitement, optic neuritis, meningitis[9], even of acute form convulsions and paralyses[7], (7) a pulmonary type with asthmatic cough and hemoptysis[1]

Effusions into the serous cavities have been described[1]

Mixed types are the rule so that any combination of the above symptoms and signs may be present Whatever the type, the characteristic nodules along the courses of the arteries constitute when they can be seen or felt, the most important physical sign and demonstration of their nature by biopsy is the most conclusive diagnostic procedure

The blood picture has been variously described Most observers report a *polymorphonuclear leukocytosis and a marked anemia* though others, notably in chronic cases find a practically normal blood state Eosinophilia occurred in 12 per cent of 38 cases[6] often it is extremely high 32 to 79 per cent[1] Blood cultures have been uniformly sterile though Goodridge[1] says that the disease apparently has been reproduced in rabbits

While the disease usually runs an acute, rather fulminant course, a few cases of long duration have been reported Perhaps the most remarkable example is that reported by Bernardinelli[3] a 57 year old textile merchant, alive after having had the disease for twenty five years who presented the extraordinary feature of freedom from symptoms during trips to his native country of Syria with recurrences on returning to Brazil He complained of difficulty in walking due to shifting joint muscle pains in his lower extremities There was slight edema of the ankles He had chills and fever worse at night, and was very weak Little nodules were found on the edges of his tongue and in the skin of the scrotum, varying in size from that of a bird shot to that of a small lentil Their appearance was preceded and accompanied by severe itching After five or six days they ulcerated and got painful The surface of the ulcers was raw

Mikulicz's Syndrome

Synonyms — Mikulicz's disease achroacytosis

Definition — A chronic benign symmetrical painless enlargement of the lacrimal or salivary glands or more typically of both

History — According to Howard on January 3rd 1888 Johann von Mikulicz Radecki described the condition which bears his name before the Society for Scientific Therapy at Konigsberg but did not publish his discovery until 189 when it appeared in the Billroth Festschrift Meanwhile in 1899 Haltenhoff reported a similar case independently as did Fuchs another one in 1891

Etiology and Pathology — Mikulicz's syndrome is not a single pathological entity so the term Mikulicz's disease is something of a misnomer If however the term is understood to refer to a clinical picture rather than to a pathological entity it may be permissible Howard assigns a large number of causes even including malignant tumors notably lymphosarcoma syphilis and leukemia and says that all gradation are found between a simple chronic inflammation and a typical leukemic involvement but others believe that malignant tumors syphilis and leukemia should be excluded and the term limited to benign types With this limitation in mind Lintz recognizes two types of lesions one a chronic inflammatory process and the other a benign lymphoid hyperplasia Tileston limits Mikulicz's disease to cases showing a chronic painless symmetrical enlargement of the lacrimal or salivary glands or both with or without moderate enlargement of the spleen and lymph nodes which run a benign course and in which the swellings do not recur after extirpation or if surgery is not employed often yield to arsenic iodides or roentgenotherapy He believes that a variety of chronic infections underlie the picture and especially emphasizes the etiologic role of tuberculosis He says that Fleischer reported one case in which iritis was present but this is not usually described and if found one would suspect the presence of the somewhat similar condition of uveoparotitis to be described in the next section of this chapter

Symptomatology — A typical fully developed case involves both lacrimal glands and all the salivary gland but any pair of glands or symmetrical group of them may be affected Usually the lacrimal glands are affected first though this is not invariable Lacrimation often is the first symptom followed by a progressive enlargement of the lacrimal glands Ptosis or exophthalmos may occur later When the salivary glands become affected dryness of the mouth usually is complained of though in the early stages occasionally this may be preceded by salivation The swellings especially of the salivary glands may

weeks is the most frequent duration Recovery has been reported[2], but is rare

Treatment — If there is any suspicion of syphilis, antisyphilitic therapy should be tried Otherwise, treatment is purely symptomatic Artificial hyper thermia has been advised as being beneficial

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culous origin of the disease but Garland and Thomson are sufficiently convinced to call it uveoparotid tuberculosis While the mortality is low, the few recorded necropsies confirm their view Some cases have shown tubercles in the myocardium Negative von Pirquet tests have been reported but Garland and Thomson state that miliary tuberculosis has been present in some of these cases, and in some others biopsy or guinea pig inoculation has proved the presence of tuberculosis Bang s theory of pseudoleukemia has been consistently discredited by blood studies, biopsy and necropsy Syphilis has been excluded Mumps has been suggested as a cause only to be rejected A number of the patients recorded had had mumps previously

As stated above the parotids and uveal tracts are the seat of chronic inflammation About half the cases of uveoparotitis show a peripheral facial paralysis often limited to the lower part of the face Taste rarely is impaired The dysphagia which occurs probably is due to lack of saliva rather than to any nerve lesion Involvement of other nerves than the facial probably is due to a polyneuritis often present in tuberculosis of varied types and is not a part of the usual picture though one of Heerfordt s patients showed sensory disturbances in the abdomen and both hands in addition to a right facial paralysis[1]

Age extremes of seven and fifty nine years have been reported though most cases have been in the second or third decades In 47 cases analyzed by Garland and Thomson there were 28 females 18 males and one whose sex was not stated

Symptomatology —Prodromes lasting from a few days to three months have been noted in less than half the reported cases They are varied in type and include lassitude drowsiness nausea anorexia diarrhea and vomiting as fairly frequent manifestations less often skin eruptions notably erythema nodosum fever joint pains paresthesias various indefinite cerebral symptoms cough amenorrhea night sweats and puffy eyes occur

The parotitis nearly always is bilateral though not necessarily symmetrical Rare unilateral cases have been described The glands are moderately swollen firm nodular and almost always painless though slight tenderness has been noted The lack of saliva causes a dry mouth and often marked thirst The glands are not attached to the overlying skin and mastication is not interfered with The swelling subsides slowly in from two weeks to three years Recurrence almost never occurs but there may be some permanent induration

The submaxillary glands are affected occasionally the sublingual rarely and both to a lesser degree than the parotids and both tend to clear up sooner In about 20 per cent of the cases there is swelling of both lacrimal glands

Bilateral uveitis has been present in all the cases described Iridocyclitis is the most constant manifestation and usually appears on one side before the other

become conspicuous by their size, but remain painless Some enlargement of the spleen and lymph nodes has been described, but is not essential

Diagnosis — This depends on the characteristic appearance of the patient, on the absence of uveitis and on the exclusion of syphilis, malignant tumors, leukemia and of all acute processes If uveitis is present, uveoparotitis, or the so called Heerfordt s disease is the probable diagnosis

Prognosis — While the condition rarely disappears spontaneously, most cases yield to treatment

Treatment — Many cases yield to arsenic or iodides Roentgenotherapy is effective in many others Surgical excision of the affected glands works a radical cure If syphilis be present, it should, of course, be treated energetically If tuberculosis be found, measures to combat it should be adopted Rarely actinomycosis has been described as a cause of the disease, and, if that occurs, iodide therapy should be pushed to the limit of tolerance

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UVEOPAROTITIS

Synonyms — Uveoparotid tuberculosis, uveoparotid fever, Heerfordt s disease

Definition — A chronic inflammatory condition of the uveal tract with enlargement of the parotid glands, often running a febrile course and frequently complicated by paralysis of the facial nerves

History — In 1909 Heerfordt[1] described the condition In 1923 Berg reviewed forty cases, and in 1933 Garland and Thomson[8] cited twenty more cases in the literature and reported three additional ones

Etiology and Pathology — Garland and Thomson have shown that a large proportion of the cases reported have shown evidence of tuberculosis, either in the structures especially involved in this disease, or elsewhere, and they have moreover, often shown a family history of tuberculosis Tuberculin therapy has been reported of benefit A few authorities still question the exclusive tuber

Miliary Fever

Synonyms —Sweating sickness miliary sweat, Picardy sweat

Definition —An acute epidemic fever having an abrupt onset and manifesting continuous drenching sweats great anxiety nervousness and a sense of oppression rapid and often tumultuous heart action respiratory distress with the subsequent development of a rash consisting of miliary vesicles and sudamina, often with an associated diffuse erythema

History —According to Hamill[1] an extensive fatal epidemic visited England in 1480 Boggs states that five epidemics swept England between 1485 and 1557 but that they spread more widely and rapidly than the more recent epidemics had a briefer duration and higher mortality and showed no rash The identity of this *sudor anglicus* of the Middle Ages and that of the miliary fever of more recent times is therefore hardly established conclusively Shaw[3] indeed believes the sudor anglicus may have been a form of relapsing fever wholly different from the Picardy sweat Osler[4] states that in 1552 Johannes Caius made an important contribution to the literature of the subject and that Hirsch gives a chronological account of 194 epidemics between 1718 and 1879 many of which were limited to a single village or a few localities According to Fussell[5] an epidemic of some extent occurred in France in 1837 and Osler[4] cites another as occurring in the same country in 1887 In 1892 Austria had a fairly large epidemic[1] In recent times the disease seems to have been confined to France Italy and Central Europe The last epidemic which the writer has found mentioned in the literature[6 7] occurred in France in 1907 The disease has not thus far been recognized in the United States A fascinating detailed history of the disease is given by Shaw[3]

Etiology —This is unknown Numerous bacteriologic investigations have been made without avail Those interested in the details should consult Hamill s article and the various source quoted by him He states that Chantemesse Marchaux and Haury noted that the infected districts had been inundated before an outbreak in 1906 that in consequence there was a pest of field and water rats and that the patients were extensively bitten by fleas They thought it possible that the rats were affected with the disease that they infected fleas and that the fleas inoculated the patients but they were unable to pursue the idea by further studies as the rats had disappeared before they began their investigations

Adults and children seem to be affected about equally though the age incidence has varied in different epidemics There is no special sex incidence

Epidemiology —The disease occurs chiefly in spring and summer and the epidemics often are very brief lasting only two or three weeks While an out

It may or may not precede the parotitis There may be pain in the eyes Posterior synechiae often develop Nodules in the iris often are noted, and some have been definitely diagnosed as tuberculous Vitreous opacities may develop with varying degrees of blindness Other ocular manifestations described have been vitreous hemorrhages, corneal herpes and opacities, keratitis, optic neuritis neuroretinitis, choroidoretinitis, glaucoma, aqueous turbidity and cataract Photophobia is fairly frequent A central scotoma has been described once Ptosis and lacrimation are rare Conjunctivitis is frequent and probably is due to rubbing the eyes The uveitis may relapse, though the parotitis does not

When facial palsy occurs it usually follows the parotitis in from a few days to six months and is of sudden onset Rarely it may precede the parotitis It usually lasts only a few weeks though one case lasted a year It has appeared after the subsidence of the parotitis

Fever, despite the name "uveoparotid fever", is present in only about half the cases Polyuria has been described, but probably is due to excessive intake of liquids brought about by the thirst which is due to the dry mouth

The blood findings are variable The blood may be entirely normal or show a moderate leukopenia or leukocytosis occasionally a moderate eosinophilia There may be a moderate secondary anemia The Wassermann reaction is negative in uncomplicated cases

Diagnosis — This depends on the picture described above Evidences of tuberculosis favor the diagnosis Other causes, notably syphilis must be excluded Mikulicz s syndrome (cf the immediately preceding section of this chapter) does not produce uveitis nor does it clear up spontaneously

Prognosis — The mortality has been given as five per cent[3]

Treatment — This involves the general treatment of tuberculosis plus special care by an ophthalmologist

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and such symptoms as prostration, anemia loss of weight, tremor cardiac palpitation arrhythmia, insomnia and general nervousness may last for months Occasionally in the acute stages of the disease sudden collapse and cyanosis may occur with death in a few minutes Fulminant cases have been described, fatal within a few hours from onset

Diagnosis — Bloomfield[8] emphasizes the following points (1) the presence of an epidemic of similar cases (2) the abrupt onset (3) the drenching sweats (4) the tachycardia with arrhythmia palpitation and precordial oppression (5) the exanthem and enanthem

During epidemics cases have been described without rash These could not be diagnosed sporadically

Differential Diagnosis — *Measles* should be differentiated by the catarrhal phenomena such as photophobia lacrimation and brassy cough as well as by the presence of Koplik s spots

Typhus Fever is louse borne shows no vesicles and gives characteristic laboratory findings

Rocky Mountain Spotted Fever has thus far a totally different geographic distribution as miliary fever does not appear to have occurred in the Western Hemisphere In addition it is tick borne and has the other differential points noted under typhus fever

Undulant Fever rarely shows an eruption but when it does it may closely resemble that of miliary fever Moreover profuse sweating is frequent palpitation often occurs and the two diseases have many nervous manifestations in common The following differential points, however should avoid confusion It is rare for a large proportion of the population of an effected area to be ill at one time wi h undulant fever The onset of that disease usually is insidious In its early stages a slow pulse is the rule whereas the pulse is rapid from the start in miliary fever In undulant fever sweating is most profuse during remissions in miliary fever when the temperature is highest The fever may be indefinitely prolonged in undulant fever lasting from many weeks to as much as a year or more but this is not always true it is brief in miliary fever rarely lasting much over two weeks The characteristic laboratory findings in undulant fever will settle the question when they are demonstrated Exposure to infected animals or their products when known should cause suspicion of undulant fever

The presence or absence of other cases of any of the epidemic diseases in question is a point to be considered in diagnosis It is doubtful if miliary fever should be diagnosed as a sporadic condition in the present state of our knowledge though we cannot say that it does not occur

Prognosis — The mortality has varied greatly in different epidemics according to Beckman[7] between two and fifty per cent In recent times the prog

break is often confined to a very small area, it is prone to attack a large proportion of the population in that area

Pathology —The skin lesions will be described under *Symptomatology* Other morbid changes noted have been early and rapid decomposition of the cadaver, dark blood with delayed or absent clotting, hemorrhages into the stomach intestines, trachea, lungs and endocardium, cloudy swelling of the spleen liver and kidneys and myocardial degeneration In fulminant cases hyperemia of the central nervous system with a slight increase in the cerebrospinal fluid has been noted

Symptomatology —According to Boggs prodromes may occur, including malaise headache vertigo muscular weakness, joint pains, dryness of the mouth and sometimes nausea and vomiting lasting a few hours or rarely a day or two, but these are often absent

Most authors describe a sudden onset with profuse sweating and fever as the primary manifestations Occasionally a slight chill may occur The temperature averages 102° to 103° F, but hyperpyrexia may occur, according to Boggs 106° or above The pulse is fast, being out of proportion to the temperature and attacks of palpitation are characteristic Epigastric pulsation with a sense of constriction or even pain and tenderness have been noted, and respiratory oppression laryngeal constriction with a sense of suffocation, insomnia, constipation prostration delirium, bleeding from the nose and other mucous membranes, cramps in the hands and legs, anorexia, great thirst and even clonic convulsions have been observed Nausea is frequent, vomiting occasional The spleen may be moderately enlarged The urine is scanty or there may be actual anuria due to the drenching sweats When these subside there may be a discharge of a large volume of urine of high specific gravity There is no leukocytosis

The sweating is the most notable feature of the disease, increasing with the height of the fever, contrary to the rule in most febrile diseases On the second, third or fourth day a rash develops, appearing first on the face neck, back, under the breasts and on the inner surfaces of the thighs A diffuse erythema usually is present but the characteristic lesions are white and red papules becoming vesicular (sudamina and miliaria rubra), and petechiae or larger purpuric spots may also occur The eruption usually is preceded by itching Vesicles may develop on the conjunctivae and mucous membranes of the nose and mouth The rash may develop quickly all over the body or appear in crops It is followed by desquamation The fever and other constitutional symptoms usually decrease with the appearance of the rash though the sweating persists for a longer period Occasionally a recrudescence of all the acute symptoms may occur during the eruptive stage In the ordinary case they clear up without recurrence within ten days to two weeks but convalescence is very slow, even in mild cases,

reported a number of other cases including both ascending and descending types one of which eventually developed a triplegia showing a variety of pathological causes [7]

Etiology and Pathology —Mills[4] later came to recognize seven pathologic types of the syndrome, whether of ascending or descending progression as follows (1) a primary unilateral degeneration of the pyramidal tracts practically a one sided lateral sclerosis later other degenerative lesions may be added (2) an early stage of disseminated sclerosis of unilateral type first described by Dr C S Potts (3) a unilateral form of amyotrophic lateral sclerosis (4) an unusual type of progression in paralysis agitans limited to one side of the body (5) an expression of a focal lesion either cerebral or spinal (6) a clinical type of cerebro spinal syphilis (7) a peripheral type of hysterical affection

To these the writer would add one more viz (8) a postencephalitic type which may be clinically identical with any of the first five types

It is obvious, then that Mills syndrome is not a single pathological entity but a symptom complex with a varied etiology and pathology

Symptomatology —The symptoms naturally vary with the type of disease present Mills first report gives an excellent description of a transition form between the first and third types and will be quoted in brief The patient was a 52 year old man Two years previously his wife and friends noted that he occasionally stubbed the toe of his right shoe scraped his right heel and showed other evidences of weakness or awkwardness of his right lower extremity The weakness increased very slowly After 18 months he noted weakness of his right arm which got worse but never so bad as his leg He could use his arm but using it made it ache He could write slowly and with difficulty and much aching Examination showed also weakness of the entire right side of his face of which he was not aware Six months after his leg began to give trouble he had some pain in the right buttock and outer thigh soon after that hyperesthesia in his right lower back and two weeks later herpes in the region of the hyperesthesia which decreased in severity but extended to involve the whole right thigh The sensory symptoms lasted only a few weeks and were considered unimportant There was a wasting of all the muscles of the right lower extremity and its movements were weak The right arm was weaker than the left Faradic contractility was retained No spasticity or contracture was found All forms of sensation were normal Tendon and muscle phenomena were somewhat exaggerated throughout the right side There was no Babinski sign No involvement of the cranial nerves was found

Here then was a chronic unilateral ascending paralysis with increased reflexes moderate atrophy but no Babinski sign and only very transitory sensory symptoms

nosis has been much less grave than in the Middle Ages, if we accept the identity of the sweating sickness of those days with the modern miliary fever

Treatment — This is purely symptomatic Liquids should be given in large amounts to compensate for the water lost in the drenching sweats, and the administration of physiologic salt solution by mouth, or, if necessary intravenously, would seem indicated to keep up the chloride content of the body Atropine may be tried to lessen the sweating Appropriate sedatives should be employed for the nervous phenomena, and in cases of circulatory collapse caffeine, adrenalin aromatic spirit of ammonia and other rapidly acting circulatory stimulants are in order

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Unilateral Ascending and Descending Paralysis

Synonyms — Mills syndrome Mills' disease

Definition — A chronic progressive, unilateral paralysis due to a variety of unilateral degenerative lesions which may begin low in the tracts involved and ascend or begin high and descend

History — In December 1899, Dr Charles K Mills[1] presented to the Philadelphia Neurological Society A Case of Unilateral Progressive Ascending Paralysis Probably Representing a New Form of Degenerative Disease In this clinic he stated that he had seen a similar case 17 years previously During the next few years Mills alone, or in association with Dr William G Spiller,

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Gerlier's Disease

Synonyms —Paralyzing vertigo falling vertigo David Gerlier's disease, Kubisagari

Definition —A disease apparently confined to certain narrow geographic limits occurring only in warm weather and affecting only those coming in contact with livestock especially when working or sleeping in stables believed to be infected characterized by a variety of nervous symptoms, including vertigo weakness muscular stiffness somnolence diplopia pains tremors etc greatly exaggerated by muscular effort and clearing up permanently as a rule after a period of rest provided the patient does not return to contact with a source of infection

History —In 1884–5 in a very small area around the western end of Lake Geneva on the boundary between France and Switzerland a disease appeared simultaneously observed by Dr David at Versoix and Dr Gerlier at Ferney Voltaire David called it falling vertigo and Gerlier paralyzing vertigo though we now know that vertigo while frequent is not always present As the term David's disease is already applied to two other conditions it is not usually employed in connection with our subject Gerlier reported his observations in 1886 and additional ones in 1891 and 1899 According to Roch[2] Gerlier's reports were confirmed by the ophthalmologists Holtenhoff and Sulzer of Geneva and Eperon of Lausanne Roch further states that in 1884 Nakano a physician in the north of Japan described the same phenomena that Gerlier had reported under the same etiologic conditions in a disease called by Japanese laborers Kubisagari which means fallen neck Professor Miura of Tokio considered it identical with Gerlier's disease though it is more widely distributed more obstinate and more recurrent Apparently Gerlier's disease disappeared from Europe about the beginning of this century but a small recrudescence was reported in 1925[3]

Etiology and Pathology —Despite considerable research the etiology of the disease is unknown It appears to be indissolubly associated with an intimate contact with livestock especially with infected stables though the writer knows of no epizootic disease believed to be transmissible to man as Gerlier's disease It seems quite certain however that the disease clears up on rest and removal from the infected areas but may reappear on returning to the old occupation and environment The geographic limitation in Europe for many years to a portion of one French Department (Ain) and two Swiss cantons

Atrophy is not a part of the one sided lateral sclerosis type The disseminated sclerosis type should eventually show a positive Babinski reflex, intention tremor sphincter disturbances, etc , and could hardly be expected to remain unilateral when fully developed The amyotrophic lateral sclerosis type would show more definite spasticity, fibrillary twitchings and more marked atrophy

The Parkinsonian type shows unilateral stiffness of the muscles rather than true paralysis a marked decrease of activity of the affected side as compared with the normal side including if the face is involved, a unilateral stare with infrequent winking of the eyelid The characteristic mask of one half the face the stiffly flexed arm the Parkinsonian tremor, would point to the diagnosis A history of epidemic encephalitis would, of course, be of great importance, when it exists

The focal type gives special focal symptoms depending on the region involved Hemiplegias due to vascular disease are not ordinarily included in the syndrome as they usually reach a stationary stage within a short time and then often show partial restoration of function rather than a steady progressive spread

The neurosyphilitic type shows the characteristic laboratory findings The hysterical type does not show the slow steady progress over a period of years common to the other types and would be associated with the other signs of hysteria and with emotional factors

Diagnosis — This is sufficiently discussed in describing the symptomatology of the various types

Prognosis — Excluding syphilitic types the condition seems to be slowly progressive Certain types, notably the disseminated sclerosis type tend to b come bilateral Focal types due to tumors, etc , will have the prognosis of the special lesion present

Treatment — The syphilitic types must of course receive anti syphilitic treatment Operable focal types should be referred to the neurosurgeon Psychotherapy is indicated for the hysterical type Otherwise the treatment is purely symptomatic Stramonium may be helpful in the Parkinsonian types

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brevity of the attack of Gerlier s disease the mu cular weakness and often the history of previous attacks will differentiate

Paralysis agitans is extremely chronic and begins insidiously That a Parkin sonian syndrome may occur in Gerlier s disease is unquestionable but it is too acute in onset to be confusing

Hysteria is excluded by the occurrence only in warm weather, the association with stables the usual type of nervous make up of cowherds and stablemen the low proportion of women due to difference in occupation the lack of demonstrable emotional factors at the time of an attack the simultaneous development of cases on farms more or less isolated from one another and the prompt recovery with rest which usually is permanent when the occupation is changed

Epidemic encephalitis offers a somewhat more difficult problem According to Roch Professor Verger of Bordeaux considered Gerlier s disease an endemic form of encephalitis subject to certain special etiologic conditions but not a sepa rate entity Recently there has been so much discussion of forms of encepha litis observed in Japan in Paris Ill and in St Louis said to be free from sequelae of consequence that further questioning may arise in our minds How ever the extraordinary limitation of Gerlier s disease to small groups of persons in restricted areas the seasonal occurrence the apparent association with livestock and stables the effect of muscular effort and rest and the frequent recurrences when work with livestock is resumed in endemic areas all seem to point to a unique condition

Prognosis —Accepting Gerlier s disease as a separate entity complete re covery may be looked for in practically every case if the patient be given a few weeks to a couple of months of rest away from infected areas Recurrence in the next warm season is to be expected if he returns to those areas and is ex posed to the same influences Otherwise recurrence is unusual Indefinite per sistence of symptoms or chronic progressive phenomena should make one suspect an error in diagnosis and consider some of the conditions differentiated above

Treatment —Rest in bed for a few weeks to a couple of months with mild sedatives if required (useful especially in the blind drunk type) removal from exposure to livestock and a permanent change in occupation when that causes exposure are essential

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(Geneva and Vaud) is very striking and suggests the operation of some very local condition as playing an essential part in the etiology As the mortality is practically nil, our knowledge of the pathology of the disease is correspondingly lacking

Symptomatology — As above stated, the disease is limited to those in intimate contact with livestock, especially men who spend part of their time in stables and who often sleep there Another peculiar feature is that attacks appear only in warm weather The chief manifestations of the disease are brought on by fatigue and repeated movements and show various combinations of the following symptoms ptosis of the eyelids weakness of muscles, especially those subjected to use just before the attack, diplopia, which may even be monocular owing to paresis of accommodation, clouding of consciousness and loss of memory for recent events, vertigo and unconquerable somnolence Other symptoms that have been noted are a tendency of the head to fall forward, pains in various parts of the body, muscular stiffness with a mask like expression suggestive of paralysis agitans, paralysis of accommodation with preservation of the light reflex (the reverse of the Argyll Robertson pupil), moderately increased tendon reflexes, transitory glycosuria, congestion of the optic papillae and a slight rise in pressure of the cerebrospinal fluid Rarely orbicularis oculi spasm has been described The disease has been reported as affecting several members of a household and recurring in attacks of diminishing severity[3] Gerlier described three chief types of attack, though naturally mixed types occur These he called the somnolent type, the apathetic type and the "blind drunk" type, the last showing an extreme degree of vertigo Despite the names "paralyzing vertigo" and falling vertigo", dizziness, while very frequent, is not always present A very important point is that rest abolishes the symptoms, but early resumption of activity brings on recurrences, often more severe than the first attack

Diagnosis — In addition to the symptoms, the occupation or history of close association with livestock, the onset only in warm weather, the involvement of those muscles subject to special use and the disappearance of symptoms after a brief rest are factors of importance to consider The disease must be differentiated from a number of other conditions

General paralysis should cause no confusion There may be a tremor of the tongue, a clouding of consciousness and a loss of memory for recent events, but there is no dementia in Gerlier's disease often there is a history of previous attacks clearing up promptly with rest but recurring with effort the pupils, if abnormal, are likely to be the reverse of the Argyll Robertson and the spinal fluid and other laboratory findings do not indicate syphilis

Brain tumor may be suggested by the mental state, staggering, diplopia, exaggerated reflexes and slight hypertension of the cerebrospinal fluid, but the

The akee or ackee is a bright red fruit when ripe the size of a small pear shaped not unlike a sweet pepper The present author has not seen the ripe fruit but Dr George L Nightengale of Jamaica N Y a native of the West Indies sent him two specimens of slightly green fruit one of them having had a portion removed to show the seeds These are shown in Fig 1 The color of these specimens on the outside was yellow with a pink blush much like that



Fig 1 Akee fruit unopened and opened size reduced about ½

of a ripe bellflower apple The seeds were a dark glossy purplish red Jordan and Burrows describe the ripe seeds as large and black the base of each being clasped by the aril or arillus a cream-colored fleshy structure which is the edible part of the fruit When the fruit is ripe the pod breaks open splitting at one end into 3 or 4 segments much in the same way as does the burr of its relative the horse chestnut The fruit is common in the Jamaica markets and usually is eaten without harm as a vegetable after boiling in water for 30 to 45 minutes Scott concludes that poisoning results from eating unopened akees those that are forced open before bursting spontaneously those from decayed bruised or broken branches and those containing soft spots

The poison is soluble in water for the pot water in which the fruit has been cooked has been found toxic Native children are especially liable to eat the dangerous fruit Jordan and Burrows prepared boiling water extracts of ripe

3 REHSTEINER, K, Erneutes Auftreten der Gerlier'schen Krankheit, Schweiz med Wchnschr, 1925 LV 410

September 1 1935

Akee Poisoning

Synonyms — Ackee poisoning, Scott's disease, the vomiting sickness of Jamaica, and isin poisoning

Definition — An acute highly fatal, toxic condition produced by eating poisonous akee fruit

History — This disease has been known for a long time in Jamaica and in West Africa The akee tree is known also in certain other islands of the West Indies in certain parts of Central America and in Demerara (British Guiana), but poisoning in these latter countries is rare apparently because the fruit is not eaten to any great extent In 1930 Manson stated that it had killed over 5 000 persons in the island of Jamaica alone since 1886 In 1943 Kean reported the first death from akee poisoning in Panama

The report of the Island Chemist in Jamaica for 1885–86 cites one case of akee poisoning His report for 1887–88 describes a family outbreak of vomiting that was attributed to the same cause An outbreak occurred in 1892 that was believed to be due to eating akees which had grown on a broken branch The first article on the vomiting sickness published in general medical literature was according to Jordan and Burrows, that by Turton in 1904, which gives a brief epidemiological discussion H H Scott Government Bacteriologist for Jamaica, in 1916 made what were the most extensive studies of the condition up to that time, hence the eponym of the disease F A G Purrhas in 1924 on page 325 of a Supplement to the Jamaica Gazette said that outbreaks had occurred with unvarying consistency for the previous 50 years or more In 1937 Jordan and Burrows and in 1938 Evans and Arnold, especially the latter, conducted studies which have thrown so much light on the subject that we may almost call their work the definitive elucidation of the disease

Etiology — Manson states that the disease formerly was considered epidemic in nature because of its tendency to outbreaks especially in the cool season but that H H Scott found the cause to be poisoning by a fruit much eaten by the natives in Jamaica which is known as akee or ackee It is called 'isin or 'ishin in West Africa and 'sese vegetal" (vegetable brain) or huevo vegetal (vegetable egg) in Central America It grows on the tree, *Blighia sapida* which is very common in Jamaica having been introduced there in 1778 from the Gold Coast of Africa Later it was planted on other West Indian islands including Cuba and Central America Scott goes on to say that when properly ripened the fruit is edible and nutritious, but if a little green or gathered from an injured branch or if the pod be opened after falling to the ground rather than opening spontaneously before falling it is highly toxic

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and unripe akees and found them equally toxic to susceptible animals, notably monkeys and cats In later experiments they found that the seeds are by far the most toxic part of the fruit, the pods somewhat so, and the arils and placentae not at all so when mature fresh fruit was used but after standing 10 days the poison is slightly diffused into the arils This may explain the poisonous effects of akees from damaged branches, the fruit being more or less isolated from its source of nutrition Fruits containing soft spots presumably have ceased their growth, and the poison diffuses in them whether they remain on their branches fall and lie on the ground or are kept too long in market or home Jordan and Burrows believed the poison to be relatively simple glucoside

Evans and Arnold believe that the akee contains a saponin which is hemolytic in immature stages of the fruit, and they consider it responsible for the disease They find it strongly hemolytic in the arillus of the unopened akee, only slightly less so in the arillus of the partly opened akee, in which the seeds are embedded and non hemolytic in the arillus of the fully opened akee provided the seeds are not embedded They find too that the toxicity varies inversely with the fat and phytosterol content, as the phytosterol fixes the saponin and renders it harm less The fruit contains less fat in the cold months (December to March) and so is more toxic in that season The disease occurs only in the cold season and is found chiefly in children in unsanitary rural communities

Distribution — In the West Indies the disease is relatively rare outside of Jamaica for two reasons because the akee is much commoner in Jamaica and because in the other islands where it does grow such as Cuba it is eaten rarely This is true also in Demerara (British Guiana) and Central America As noted above it also occurs in West Africa under the name of isin or ishin There it is said to have been used for homicidal hospitality if a native had certain undesirable ' friends he might invite them to a meal serve isin in its toxic state to them avoiding it himself and in a short time he would not have any of those unde sirables left

A harmless fruit from the tree *Melicocca bijuga* in Barbados sometimes is miscalled akee its correct name being 'genip' or 'ginep' This must not be confused with the true akee (personal communication from F N Grannum Acting Chief Medical Officer Barbados under date of March 4 1944)

Pathology — Manson states that at necropsy hyperemia of the viscera is found with minute insterstitial hemorrhages and fatty changes in the liver and kidneys and to a less degree at times in the pancreas and heart muscle Jordan and Burrows and also Kean are in substantial agreement with this In experimental kittens Evans and Arnold found the kidneys hemorrhagic the liver large and degenerated, the lungs collapsed and hemorrhagic the bladder very distended with clear fluid and the brain hemorrhagic Microscopically they report tubular nephritis which was extensive and diffuse, most marked in the cortex, diffuse

cloudy swelling of the liver especially at the periphery with some fatty degeneration while the lungs were bronchitic with seropurulent fluid in the alveoli and bronchioles suggesting aspiration pneumonia

Symptomatology — Manson describes the onset as sudden with abdominal discomfort and vomiting These symptoms appear 2 or 3 hours after eating the toxic fruit The patient then may seem to recover for a short time and even fall asleep but within a few hours or even less time vomiting recurs and becomes of a definitely cerebral type and unless treatment is prompt convulsions or coma soon develop and the patient usually dies quickly The temperature may be normal or slightly above or below normal the pulse rate a little above normal till near the end the respiratory rate from 26 to 30 per minute Often the pupils are slightly dilated but they react well There is no muscular rigidity except with a convulsion Manson says that death has occurred within 1½ hours after the onset of symptoms although the average duration of life in fatal cases is 12 hours If the patient lives recovery usually is complete within 24 hours after onset according to Manson but Jordan and Burrows mention death in 3 to 4 days

Diagnosis — This depends on the symptomatology plus the history of having eaten the fruit or its pot water a very short time previously

Prognosis — Manson states that the mortality is between 80 and 90 per cent

Treatment — Manson advises in the primary stage of the vomiting an emetic plus prompt gastric lavage with some alcoholic liquid such as whiskey as alcohol renders the poison harmless by precipitating it

Prophylaxis depends on educating the people to eat only the edible parts of properly matured and fresh fruit which has opened spontaneously and shows no embedded seeds and to recognize and avoid the poisonous stages and types of akee and on keeping little children and mental defectives from getting poisonous fruit

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discovered the trouble only after several days When fighting with his playmates he would bite his own tongue till it bled so that it became badly scarred He would fight older boys without complaining even though he was dripping with blood He ran about for some months on fractured metatarsals Once he sat on a hot radiator until he was burned deeply over the sacrum While in a hospital for this burn he complained one time of abdominal pain He had scars all over his body His cervical axillary and inguinal lymph nodes were enlarged His cranial nerves were normal

He felt light touch everywhere and also slight differences in temperature and could distinguish sharp from dull yet felt no pain Even squeezing his testicles was painless and caused no increase in the pulse rate Pinching his neck did not dilate his pupil Pressure over the supraorbital and ulnar nerves was painless His recognition of passive movement position vibration his two point sense and stereognosis were all normal His eyes showed corneal opacities posterior capsular cataract and dense vitreous opacities due to old injuries His intelligence quotient was said to be 104 and he was an average 3rd grade student

He was right handed right-eyed and right legged In addition to his analgesia he had a mild congenital word blindness with deficient appreciation of the orientation of words with reversals of the was for saw type His reading index was 40 per cent of normal He also showed low scores in auditory discrimination His personality seemed quite normal he did not like to fight but older boys were always trying to put him in the hospital He had normal vasomotor reflexes His bones were normal roentgenologically except for old fractures and a Koehler s congenital dystrophy of the scapula Blood Wassermann Mantoux test and urinalyses were negative Rather extensive blood chemistry studies gave essentially normal findings The spinal fluid was normal in every respect

The boy behaved well in hospital and showed no desire to fight no bravado and no pride in his condition Ford and Wilkins felt that he seemed to be developing some sensitiveness to pain but offered no evidence of this beyond the fact that he began to fear that he might be hurt and refused tooth extraction without an anesthetic

The second case studied by the above authors was an $8\frac{1}{2}$ year old boy who showed many scars at the age of 3 years and whose objective sensory findings were the same as those of the first patient although the x ray showed no signs of old fractures This boy was emotional had night terrors temper tantrums and enuresis and was given to masturbation He would fight big boys but feared dogs At the age of 2 years

Critchley's own patient was a pale faced weedy young man who felt pin pricks but said they were nothing much Lancing a whitlow and extracting teeth without anesthetics had caused no discomfort Once he had an umbrella broken over his head in an argument without any pain There was a noticeable discrepancy between his insignificant physique and his apparent fortitude

Dearborn described the case of Edward H Gibson *known in vaude ville* as the human pincushion He was born in Prague and was artless and sincere For 4 years he was a musician in the United States Marine Corps The only pain he ever felt was an occasional headache He had many injuries including a blow on his head with a pickaxe a severe hatchet wound laying his head open a revolver bullet passing through an index finger a fractured fibula and a burn of his hand on a gas stove detected by the smell of burning flesh all with practically no pain though some had caused a certain amount of shock An attack of acute otitis media troubled him so little that he did not stay away from school Bilateral pneumonia was painless In his vaudeville act he would invite anyone to stick pins in him anywhere except in the abdomen and groin Sometimes as many as 60 pins would be *driven in* up to their heads He had a standing offer of $5 000 to any physician who could detect any sign of pain during these procedures Once he staged a crucifixion act but when the first nail was driven through the palm of one hand certain members of the audience collapsed and the act was called off No evidence was found of any nervous or mental disease and Dearborn states specifically that hysteria was excluded satisfactorily

Schilder in discussing this case mentioned another showing a familial incidence in which ordinarily painful stimuli caused no pupillary reaction or change in blood pressure This patient showed an extreme degree of algolagny however

Ford and Wilkins reported 3 cases in children The first case was that of a 9 year old boy who had had numerous injuries including fractures extensive burns and lacerations of the cornea Aside from the analgesia no objective evidences of disease of the nervous system were found The boy s parents noted when he was quite young that he did not seem to notice injuries as other children did The usual falls and blows of childhood never made him cry or show other signs of pain As an infant he chewed his fingers till they bled and became scarred and deformed At the age of 2 years he broke a fibula and continued walking about apparently without pain At 5 years of age sand was thrown in his left eye and the cornea ulcerated but he did not complain and his mother

Essential Fructosuria

Synonym — Essential levulosuria Just as the term glycosuria is used more commonly than the synonymous dextrosuria so fructosuria is more widely used in present day literature than is levulosuria

Definition — Essential fructosuria may be defined as an extremely rare anomaly of metabolism characterized by the symptomless excretion of a fairly constant proportion of the ingested fructose

History — Rynbergen Chambers and Blatherwick state that the first case of probable essential fructosuria known to them in the literature is that reported by Zimmer and Czapek in 1876 Most of the reports have appeared within the last two decades Lasker collected 58 cases all told up until 1941 but she believes that 18 of these fail to satisfy the criteria for essential fructosuria Some e g were in diabetics and the levulose could have been formed from dextrose

Etiology and Incidence — The etiology of this condition is unknown *At present it is looked upon as an inborn error of metabolism* Marble and Smith of Joslin s clinic presume that the liver normally removes fructose from the blood storing it as glycogen and that in essential fructosuria this special function of the liver fails to a degree without other signs of hepatic dysfunction It may be remarked in passing that the constancy of the degree of failure as measured by the constancy of the ratio of the amount of fructose excreted in the urine to that ingested usually from 13 to 14 per cent being excreted no matter what the duration of the condition seems extraordinary on any etiological hypothesis thus far advanced Silver and Reiner believe that there is a specific enzymatic deficiency in the liver impairing its ability to fix levulose as glycogen

Essential fructosuria has been reported at all ages although it is discovered *more frequently before the age of 30*

In geographic range essential fructosuria is spread widely over Europe and also occurs in the United States though very few cases have been reported in this country

Lasker considers the condition a recessively inherited one In 19 families of patients with essential fructosuria studied by her 10 showed a familial incidence The incidence of the condition in the general population is exceedingly low being estimated by Lasker as about one in a *million*

Pathology and Pathological Physiology — As the condition is completely benign no pathological alterations in structure have been demonstrated

he had had three convulsive seizures but these were the only ones known throughout his life up to the time of examination His father had been backward at school was a reformed alcoholic fought a lot and was very jealous of his wife who feared him The boy s mother had had temper tantrums and convulsions as a child and had spent four years in an institution for defective children At the age of 12 her mental age was 6

The third patient of Ford and Wilkins was a 7 year old girl who had been thought hysterical because of her analgesia

Diagnosis — This is made by excluding additional factors present in other diseases showing analgesia The lack of atrophy contractures etc and the completely generalized analgesia discovered very early in life should exclude syringomyelia neuritis etc The absence of the initial pains and hyperesthesia and also of the muscular eruption early in the disease and the fact that the analgesia is generalized from the beginning should readily distinguish the condition from anesthetic leprosy In hysteria the analgesia rarely is completely generalized the symptoms are variable there are evidences of marked instability of personality psychogenic factors are present and the condition is not congenital these characteristics are sufficient to distinguish between the two

Prognosis — In general the condition seems to be permanent although Ford and Wilkin s first patient suggested to them the possibility that he might be developing some sensitivity to pain

Prophylaxis and Treatment — Obviously no prophylaxis of the condition per se is possible but prevention of the secondary lesions is important The patient should be taught to avoid injury so far as possible to search frequently for evidences of painless injuries swellings etc and to have all such conditions given prompt expert attention In the present state of our knowledge the basic condition is not amenable to treatment

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essential fructosuria They also cite Edhem Erden and Steinitz as obtaining similar results with reference to blood lactic acid in a patient studied by them Silver and Reiner note that the ingestion of as little as 1 gram of fructose will produce fructosuria in a patient They also note that the blood glucose tends to fall as the blood fructose rises although the total blood sugar usually is above the normal level Steinitz noted that after the intravenous injection of fructose its removal from the blood was delayed considerably beyond the normal time The patient of Heeres and Vos showed a trace of acetone in the urine but no diacetic acid

Symptomatology — The only symptom is the objective one of fructosuria which bears a constant relation to the fructose ingested Polyuria does not occur or if it does it is due to some coincidental cause. Many of the reported cases have a long history of sugar in the urine even up to 25 years Essential fructosuria does not progress or change in any way in the course of time Rivoire and Bermond reported a patient showing severe neuritic pains and thought the fructosuria might be a factor in producing the neuritis but as their findings are unique it seems much more likely that the neuritis was merely coincidental and not the result of fructosuria

Diagnosis — Heeres and Vos recognize three types of fructosuria (1) a special alimentary form occurring in diseases of the liver parenchyma such as hepatic cirrhosis catarrhal jaundice hepatic syphilis etc (2) in association with glycosuria as in diabetes mellitus (3) the true essential form much the rarest type

The usual clinical reducing tests for sugar in the urine positive for both do not distinguish between glucose and fructose Yeast will ferment it in the urine The urine shows levorotation which disappears after fermentation The Schwanoff reaction with the proper precautions is positive The methyl phenyl osazone can be isolated and its chemical and physical constants be determined Heeres and Vos add another criterion of importance and that is that liver parenchymal disease should be excluded using the galactose tolerance test for this purpose probably other tests of liver function would serve as well

Essential fructosuria should be sought for in patients with supposed diabetes who give a long history of uncontrolled sugar in the urine without impairment of health and in any supposed diabetic in whom insulin fails to cut down the sugar in the urine

Prognosis and Treatment — No treatment is indicated for this condition which as already noted is wholly benign

In connection with the pathological physiology of the condition Heeres and Vos note fourteen points as follows

1 Fructosuria disappears on a fructose free diet i e a diet containing neither fructose itself nor fructose yielding polysaccharides This includes the fasting state Fruits most vegetables honey and cane sugar are the chief fructose containing foods

2 Independently of the amount of fructose ingested a fairly constant part of it averaging about 14 per cent is excreted in the urine The reason for this is unknown

3 Contrary to normal results the administration of fructose leads to a considerable rise in the blood sugar content due almost entirely to fructosemia

4 After the administration of fructose in divided doses as much is excreted as when the same total amount is given in a single dose

5 The intravenous administration of fructose produces fructosuria of the same degree as the oral administration

6 Insulin has no influence on fructosuria

7 Fructose given in combination with other sugars or as a fructose-yielding polysaccharide results in a more marked fructosuria than when the pure fructose is given alone

8 Insulin does not produce fructosuria probably because it is not broken up in the intestine into fructose

9 The metabolism of dextrose galactose maltose and sucrose is not disturbed

10 Sorbose a ketose like fructose the only known *sugar that* is excreted normally in the urine in small quantities was excreted in large amounts in their case

11 After the administration of fructose there is little or no rise of the respiratory quotient contrary to what is seen under normal conditions

12 Fructose injected intravenously immediately after the solution has been prepared leads to a greater degree of fructosuria than does a solution prepared some time prior to injection Heeres and Vos attribute this to the transformation of β fructose into α fructose in the solution allowed to stand

13 Crystalline fructose given by rectum causes a more marked fructosuria than does fructose given by mouth

14 They consider that a connection probably exists between items nos 12 and 13 and multirotation

Rynbergen Chambers and Blatherwick state that no appreciable rise in blood lactate occurred following levulose ingestion in two persons with

However the familial incidence of a great majority of the cases and the marked similarity of the cases described one to another seem to justify in some measure a consideration of the Rothmund Werner syndrome as a fairly definite clinical entity Eventually it may become clear that those various associated conditions which are etiologically connected with scleroderma are all vascular in origin perhaps due to a panarteritis but it is difficult at the present time to synthesize all of them into a common etiological picture

In 1868 Rothmund described three families containing fourteen children in all five of whom had a marmorization of the skin with telangiectases and bilateral juvenile cataracts and one more child had the same dermatosis without the cataracts Most recent authors believe these children to have had the same condition as that present in the four cases in one family described by Werner in 1904 in which the dermatosis was definitely identified as scleroderma Oppenheimer and Kugel however disagree with this and consider Werner s report the first record of this syndrome which therefore is variously known as Rothmund s syndrome the Rothmund Werner syndrome or Werner s syndrome In 1939 Agatson and Gartner collected 32 cases from the literature

Only a brief description of the symptoms may be given here full details being available in special works on dermatology ophthalmology and endocrinology The scleroderma or poikiloderma often begins as a spreading patch on a lower extremity resembling a simple callus if it starts on a sole and may come to involve a major portion of all the extremities and also the face Often however it is limited to a portion of the lower extremities especially the distal parts Chronic ulcers of the toes frequently develop

At times an arrest of development and growth may be the first thing noted The age of onset of the syndrome has varied from 4 to 55 years The skin lesions usually but not always precede the cataracts In the case described by Flandin Poumeau Delille and Olivier the cataracts seemed to become arrested while a moderate degree of vision remained but as a rule they mature and can be removed surgically In the male potency is the rule but fertility is low The graying of the hair and alopecia may occur in childhood

As a rule the diagnosis is obvious at a glance If only the scleroderma or poikiloderma has developed and no cataracts are present positive diagnosis is impossible though it may be suspected if others in the family show the typical syndrome In the very rare cases in which cataracts do not appear until the patients reach a suitable age for the

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THE ROTHMUND WERNER SYNDROME

This syndrome may be defined as a heredofamilial disease characterized chiefly by the development of sclerodermatous or poikilodermatous changes which tend to affect especially the extremities and with somewhat less frequency the face by intractable ulcers of the toes by bilateral juvenile cataracts by hypogonadism by premature graying of the hair and by a tendency to alopecia along with premature arteriosclerosis Telangiectases also are common Incomplete forms showing only a part of this complex symptomatology are common

It has seemed questionable to this writer whether any special group of conditions associated with sclerodermatous changes should be elevated into a special syndrome and given a particular name for the number of conditions associated with scleroderma are legion Some are obviously coincidental affections others are no doubt etiologically connected while still others are of uncertain relationship At least 60 associated conditions are mentioned by title along with scleroderma in the Quarterly Cumulative Index Medicus including such widely divergent conditions as calcinosis dermatomyositis Raynaud s disease pluriglandular dystrophy muscular dystrophy leukemia muscular atrophy fungoid mycosis parkinsonism myastheniagravis erythromelalgia Addison s disease arsenic in the urine thyroid tumor etc In many instances two or more such associated conditions are described as occurring along with scleroderma in one patient

primary infection Still later bullae and superficial ulcers may appear Thrombophlebitis also may occur and this should be sought for always especially when one leg is more swollen and painful than the other The condition is found in young and old of both sexes but is especially common in elderly women and obese persons Deck chairs are supplied in many air raid shelters in England Prolonged pressure for 24 hours or more from the wooden crossbars of these chairs on the thighs or popliteal vessels appears to be the essential etiological factor

Simple pressure edema of the feet without the other phenomena mentioned above has been noted after prolonged trips by air as from Cape Town to London and also after long rides in certain modern day coaches such as are found in some American stream lined trains when the traveller occupies a seat day and night for perhaps 48 hours or more as in going from Chicago to the Pacific Coast Usually this simple pressure edema is of no importance as it clears up spontaneously after the trip is completed without any special inconvenience to the patient

In the more severe form known as shelter legs however the patient must be taught to elevate his feet in such a way that there is no undue pressure on his legs for several hours out of the 24 if not by night then by day Thrombophlebitis if it develops under these circumstances of course requires the usual prolonged care given to this condition

The present writer once had a patient an elderly man who developed thrombophlebitis and edema believed to be due to pressure on his legs from sitting in his home on one chair with his legs on another in such a way that the edge of the seat of the chair on which he had his legs made considerable pressure on them Only when he developed a pulmonary infarct did he seek medical aid and then despite rest in bed and hospital care he developed signs of thrombophlebitis in his other leg an infarct in his other lung and finally a massive pulmonary embolism which killed him a few moments after it developed

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EDITORIAL Shelter legs Lancet 1940 II 72

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development of the ordinary type of senile cataract the slit lamp will decide the matter according to Sezary Favory and Mamou

As a rule the condition is steadily progressive but it may become arrested in any of its phases The cataracts are to be treated on the usual ophthalmological principles Other treatment is of little avail

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Shelter Legs

This is merely a special form of pressure edema of the legs followed by certain dermatological changes in which the skin of the legs becomes red and painful suggesting an early cellulitis but without evidence of

hardly explains the extraordinary intensity of the process. Others suggest a toxi infectious origin but have proved nothing

Histologically in the Pick type the three outer layers of the cortex are likely to be especially involved in the Alzheimer type the deeper layers In the latter type so-called senile plaques occur in great profusion as noted above The findings resemble those of senile dementia except that they are more diffuse and intense Plaques are absent in the Pick type and form the readiest means of differentiating the two types pathologically

Symptomatology —Critchley[a] quotes Schneider as recognizing three stages of Pick's type and the same may be applied to Alzheimer's type for clinically as above noted the two types are indistinguishable These are 1 A phase of restlessness in which the patient becomes exalted and euphoric and often disordered in conduct 2 A progressive demential stage to which focal manifestations are added 3 A terminal stage of cachexia and complete dementia with contractures bedsores incontinence and often convulsions The onset of either type usually is in the 5th or 6th decade but may occur much earlier as noted The mental symptoms come on insidiously as a rule

Lowenburg and Waggoner[1] have reported a case so beautifully in detail (Alzheimer type) that it seems worth while to give their essential findings here The patient was a printer unusually young at onset being only 32 He was one of a familial group and was first interviewed not regarding his own condition but that of his sister At that time he seemed peculiar and rather unbalanced mentally He had seemed quite normal up to a few years previously being good natured sociable industrious and thoughtful of others He had become nervous and excitable in the recent past and talked about being nervous and shaky

During the next year he became more excitable and so forgetful that he lost his position He would brood over this and cry when he failed in some task At the age of 34 he was examined and was obviously entering the second stage for he showed slight nystagmus on lateral deviation to the left The Kahn test for syphilis was negative

During the next two years he deteriorated gradually becoming drowsy during the day making childish requests being unable to remember dates and places and often wandering from home He had little insight into his condition but thought his nerves were shattered He would laugh or cry without provocation and during one of his crying spells he complained of sharp pains in the head

On physical examination at the age of 35 he showed no evidences of arteriosclerosis His blood pressure was 108/62 His pupils were sluggish and he had some tremor of the fingers on extension All reflexes were normal He cooperated poorly and was confused showing a marked loss of memory for both

Atrophy of Gray Matter of the Brain

Synonyms — Arnold Pick's disease Alzheimer's disease

Definition — A chronic degenerative affection of the gray matter of the brain characterized clinically by disorders of behavior progressive dementia various focal manifestations and a terminal stage of cachexia, complete dementia contractures bedsores incontinence and at times convulsions Pathologically there are two distinct types Arnold Pick's type and Alzheimer's type They are indistinguishable clinically

History — In 1892 Arnold Pick[1] reported two cases of dementia in elderly people lacking marked evidences of arteriosclerosis but showing a symmetrical atrophy of certain areas of the cerebral cortex without the ordinary senile changes As other cases were recorded the so called "Pick's disease" came to be recognized as a form of "presenile dementia" characterized anatomically by circumscribed areas of cortical atrophy

In 1906 Alzheimer described to the Southwest German Psychological Congress a form of "presenile" dementia showing an extraordinarily intense pathological process Senile plaques were extraordinarily profuse more so than in the most advanced cases of ordinary senility A considerable number of such cases have since been recognized

Etiology — This is unknown Originally thought to be a peculiar type of cerebral arteriosclerosis without the ordinary manifestations of that condition in the blood vessels this idea has been abandoned, and the present view is that it is a degenerative process of unknown nature Formerly thought to be limited to the presenium it is now known to occur much earlier though this is rare The youngest patient whose case the writer has found reported in the literature was 15 years old[3] Familial involvement has been noted in the Alzheimer type[4] but is not the rule Alcoholism and consanguinity of parents also have been reported[4] but are not essential to the picture

Pathology — The Arnold Pick type has been described as a circumscribed symmetrical atrophy of certain areas of the gray matter without the usual changes observed in the senile brain and without the ordinary evidences of arteriosclerosis There is some general atrophy of the brain as a whole but the striking manifestations are cortical Most often the temporal lobes are chiefly affected but the cortical areas of any of the lobes including the insulæ may be especially involved apparently always in a more or less symmetrical manner

The Alzheimer type tends to be more diffuse and shows certain special features in its histology The basal ganglia and cerebellar cortex may be involved Some authorities look upon it as a form of premature senility but this

proper, in which focal signs plus intellectual decay are associated with distinct types of histologic change in the cerebrum Two disorders in particular belong here Pick s disease and Alzheimer s disease Those rare and curious cases of cerebral gliosis of the presenium described by Spielmeyer and by Kraepelin should be included also

Diagnosis of these diseases must be by the elimination of arteriosclerosis brain tumor syphilis, epilepsy etc.

How shall we distinguish one of these diseases from the other? (i e Pick s from Alzheimer s) It is a question whether we can without the crudity of brain puncture and histologic examination

Encephalograms are of doubtful value The so-called presbyophrenia or simple apathetic state is probably an early form of one or the other of these conditions *Obviously the history of the case will exclude many of the conditions to be eliminated* The focal signs of *brain tumor* usually will be suggestive and where doubt exists encephalography may differentiate

Encephalitis may not give a history of the infection at onset and when it does not may be difficult or impossible to differentiate *Disseminated sclerosis* usually begins at a younger age though as noted the atrophies under discussion occasionally may begin in youth The degree of dementia usually is *less in a corresponding stage of disseminated sclerosis* *Syphilis* will be excluded by laboratory findings as will *uremia* *Hypertension* should be excluded *Arteriosclerosis* must be eliminated by physical examination and with the ophthalmoscope *Cerebral thrombosis* is unlikely to occur in the absence of arteriosclerosis and does not show the slow steady progression of the atrophies

Prognosis — Both the Pick and Alzheimer types are typically chronic progressive, incurable and eventually fatal Usually the course covers some years but in exceptional cases may be quite rapid The Pick type has been described as *lasting twelve years and the Alzheimer type twenty years*[a] but this is much longer than is ordinarily the case Three to six years would seem a fair average duration

Treatment — Treatment usually must be institutional in the later stages at least as the patients are irresponsible and eventually become unable to care for their most elemental needs In the early stages appropriate sedation is indicated to allay nervousness and excitement. Nothing is known which influences the course of the condition favorably

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remote and recent events He could not do simple sums or recall his wife's name He was apprehensive of difficulty and would make excuses for his failures He was practically unable to write

A year later he had a convulsion lasting several minutes, crying out, rolling his eyes, making convulsive movements of his arms and frothing at the mouth He became apathetic and showed irregular myoclonic movements, especially in his face and in the fingers of his left hand His pupils were normal at this time, and he could turn his eyes completely to the right but not quite completely to the left Cranial nerves otherwise were normal Eye grounds were normal Tendon reflexes were normal Abdominal reflexes were normal on the left decreased on the right Muscle tone was increased in all his extremities and there were suggestions of positive Babinski, Oppenheim, Gordon and Chaddock signs on the left He walked slowly with both arms flexed at his elbows in front of him without swinging them He showed a definite tendency to fall to the right and some incoordination in using his right arm Soon after this he had another convulsion lasting a few minutes, and after that he failed rapidly and became much less active and restless For several days before his death he exhibited a generalized spasticity with spasmodic contractions of the extremities He was 37 years old at death

Other patients have shown symptoms suggesting an apoplectic stroke, severe headaches, delusions incontinence of urine and feces drooling of saliva, fever (102° F) weak irregular pulse dysphagia, inability to hold things in the hands, signs of pyramidal tract irritation, tremor of tongue, marked speech defects hallucinations etc

Nervousness irritability and excitability in the early stages, progressive memory loss and finally complete dementia with loss of contact with the outside world, so that the patients led a vegetative existence, are symptoms common to practically all cases, and they are associated with a great variety of focal signs depending on the location of the maximum changes

Diagnosis — The differential diagnosis of these conditions was so ably discussed by Critchley at a meeting of the Royal Society of Medicine of London in 1933 that it seems worth while to quote from his remarks

"A progressive intellectual deterioration in a hitherto healthy person of middle age indicates of necessity cerebral change of demonstrable character There are three common types neoplastic, syphilitic, arteriosclerotic There are smaller groups due to the progressive dementia of chronic epilepsy and chronic toxi infectious processes especially alcoholism and uremia Trauma will account for a small number 'Certain progressive and longstanding disorders of the nervous system may show corresponding mental deterioration such as Huntington's chorea, epidemic encephalitis and disseminated sclerosis

"There remains a mysterious group of disorders, the presenile dementias

proper in which focal signs plus intellectual decay are associated with distinct types of histologic change in the cerebrum Two disorders in particular belong here Pick s disease and Alzheimer s disease Those rare and curious cases of cerebral gliosis of the presenium described by Spielmeyer and by Kraepelin should be included also

Diagnosis of these diseases must be by the elimination of arteriosclerosis, brain tumor, syphilis epilepsy etc[*]

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Progressive Centrolobar Sclerosis

Synonyms — Diffuse sclerosis, lobar sclerosis, familial centrolobar sclerosis, Pelizaeus Merzbacher disease Schilder's disease, Schilder Flatau disease Schilder Foix disease, encephalitis periaxialis diffusa, encephaloleukopathia scleroticans progressiva, leukoencephalite subaigue a foyers successif, sclerose intracerebrale centrolobaire et symmetrique

Definition — A diffuse progressive disease affecting especially the white matter of the brain beginning in early life and often familial in incidence It seems to be a fairly definite pathological entity but presents an extremely varied clinical picture depending on the areas chiefly involved

History — In 1885 Pelizaeus[1] described five cases of a familial central nervous disease of a previously unrecognized type, considering them to be a hereditary form of multiple sclerosis About twenty three years later Merzbacher was sent a brain for study which showed such unusual findings that he traced the history of the case and found that six siblings were afflicted with a similar condition, and that this family was related to the family studied by Pelizaeus in 1885 Merzbacher then published his observations[2] In 1912 Schilder[3] described a condition which he called encephalitis periaxialis diffusa which closely resembled the Pelizaeus-Merzbacher disease though he considered it a separate clinical entity

Etiology — This is unknown Merzbacher considered the changes essentially developmental Schilder considered his cases infectious and toxic in origin Merzbacher reported a strong hereditary basis with a tendency to a sex linked transmission such that males usually were affected from unaffected mothers, though exceptions have been found to this rule In the afflicted families the mothers would pray that their offspring might be girls rather than boys because of the preponderance of the disease in the male sex Merzbacher traced fourteen cases, including the five originally reported by Pelizaeus through four generations and noted that twelve were males and two females Schilder did not find a hereditary basis in his cases, but later observers have

stated that the so-called Schilder's disease can show a hereditary tendency, and Symonds[4] in particular believes it may be identical with the condition described by Pelizaeus and Merzbacher Lauritzen and Lundholm[5] are not sure that Schilder's disease is an entity to be distinguished from all other diseases

Age is an important predisposing factor as practically all cases begin in early life, some even in infancy

Pathology —Scheftel[6] notes some disagreement of authorities regarding the essential nature of the disease process He summarizes Merzbacher's findings as follows symmetrical atrophy of the white matter of both hemispheres and cerebellum, the degeneration of the centrum ovale spreading from the ventricles toward the cortex Myelin sheaths were absent or fragmented and axis cylinders either gone or changed There were small areas which appeared on cross-section as dots and lines the so-called Markinseln with intact nerve fibers The cortex of the hemispheres and corpus dentatum of the cerebellum were unaffected as were the arcuate fibers The only marked increase in neuroglia was in the thalamus The corpus callosum and the fornix were shrunken the anterior commissure well developed but the corona radiata and association centers were not severely affected The frontal occipital and temporal lobes were involved chiefly The internal and external capsules the brain stem and pons were on the whole, normal Merzbacher considered the process a congenital maldevelopment of the white matter rather than a degenerative or destructive process in the main hence the subtitle of his paper aplasia axialis subcorticalis congenita

Spielmeyer who studied the brain of a sister of the patient whose brain was sent to Merzbacher did not wholly confirm Merzbacher's findings He considered the process essentially degenerative in nature and found marked involvement of the white matter not only of the cerebrum basal ganglia and cerebellum but also of the brain stem pons medulla and cord In the cord the gray matter was involved in places and there were a few scattered lesions in the cortex.

Schilder in his cases found in addition to the centrolobar sclerosis an infiltration of the blood vessels with lymphocytes and granular cells a disturbance of the lymph circulation and many fat globules and large glia cells Symonds[4] points out that the axis cylinders do not escape so that the term encephalitis periaxialis is somewhat misleading Wechsler[7] states that hydrocephalus may occur

Symptomatology —The children appear normal at birth Sometimes as early as three months of age nystagmus and abnormal head movements appear which may disappear later In general two stages of the disease may be recognized In the first stage spasticity incoordination of the extremities

nystagmus and speech disturbances are prominent There is usually difficulty in walking, if the child is old enough to walk, the knee jerks are increased, the Babinski sign is positive, ankle clonus is likely to be present, ataxia, intention tremor or athetosis may occur, and there may be a decrease or absence of the abdominal reflexes Blindness of cerebral type without changes in the fundi occurred in Schilder's cases, as did certain auditory disturbances In the second stage paresis and contractures appear, also psychic changes with eventual mental deterioration, a staring facies and sometimes trophic disturbances such as cyanosis of the extremities and osteomalacia These symptoms vary greatly in individual patients, but in all the progress is towards mental deterioration and physical helplessness In Merzbacher s cases a slow and scanning speech, foolish grimacing facies, ataxia, intention tremor, athetosis, choreiform movements, spasticity and progressive dementia were the outstanding symptoms No sensory or electric changes were found and no sphincter disturbances, though later observers have noted the last named symptom Pallor of the optic discs was described in one case by Pelizaeus, but this was not noted in the other cases

Schilder s cases ran a rather rapid course and showed headache, auditory disorders, paralysis, psychic deterioration, blindness, convulsions and sphincter disturbances Merzbacher reported a patient showing symptoms at the age of twenty eight who died at fifty two but this is unusually old Most cases begin in infancy or early childhood and do not reach adult life

Canavan[8] reports a case showing macrocephalus and states that it is necessary to separate macrocephalus due to diffuse degeneration of the brain from that due to hydrocephalus or tumor, but then states that at autopsy an excess of fluid was found in the subarachnoid space

Diagnosis —An essential point in diagnosis is that the patient must show no signs of brain disorder at birth, thus excluding birth injuries, the ordinary developmental defects, etc Syphilis must be excluded Multiple sclerosis rarely appears in as early an age period as does centrolobar sclerosis A case of centrolobar sclerosis first appearing in late childhood or young adult life may be impossible to differentiate from multiple sclerosis, and conversely, a case of multiple sclerosis appearing in early childhood might be equally deceptive A familial incidence strengthens the diagnosis of centrolobar sclerosis but is not essential to it The striking variety of symptoms, though all do not appear in a given case, including speech disturbances, ataxia, athetosis intention tremor, nystagmus, clonus, spasticity psychic peculiarities, blindness auditory disturbances, with eventual paralysis contractures and mental deterioration in a young child normal at birth, in whom syphilis has been excluded, will strongly suggest the diagnosis

Prognosis —This is bad The disease steadily progresses, much more rap-

idly in some cases than in others but all cases prove fatal in the end though often some intercurrent disease or accident such as inhalation pneumonia concludes the chapter Occasionally a matter of weeks life is often one of months or years

Treatment — There is no known effective treatment Where proper care cannot be given the child at home institutional treatment should be advised

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Von Gierke's Glycogen Disease

Definition — A chronic disease with a familial tendency beginning in infancy or childhood characterized by an excessive accumulation of glycogen in various organs of the body which gives rise to an extreme degree of enlargement of one or more of the organs involved

History — In 1923 Worster Drought[1] demonstrated a patient with this disease before the Royal Society of Medicine in London characterizing the condition as a case of enlarged liver with persistent acetonuria and diaceturia He did not recognize the real nature of the disease however until after von Gierke's epoch making paper in 1929 in which the idea was advanced now generally accepted that the essential pathology is an excessive accumulation

of glycogen in the tissues involved This led Worster Drought in 1933 to publish further observations on the patient demonstrated ten years previously and to recognize the condition as that described by von Gierke[3] In 1932 Bischoff[4] and Putschar[5] described the cardiac form of the disease The disease is rare, for in 1935 Lindsay, Ross and Wigglesworth[6] reported a case and cited Humphreys and Kato as claiming in 1934 that there were but 15 proved cases on record

Etiology — This is unknown All we can say is that there is a profound disturbance of glycogen metabolism A definite familial tendency to the disease seems to be established Syphilis is not a factor It is interesting in comparison with this condition that childhood diabetes mellitus, if it leads to dwarfism, shows striking liver enlargement, whether this is due to glycogen or fat deposit, is not known

Pathology — The liver is most frequently affected and may become huge enormously distending the abdomen It is smooth, of very firm consistency, though not hard, without nodules or depressions and is uniformly enlarged throughout its extent with well defined edges It may occupy the major portion of the entire abdominal cavity reaching to the iliac crest on the right and the umbilical level on the left Smith and O Flynn[7] describe the color as pale buff, showing on close inspection very minute pale yellow areas distributed evenly throughout They characterize the cut surface as smooth, homogeneous, very dense and somewhat translucent The bile ducts are not dilated The gall bladder is not affected nor is the spleen Ascites does not occur nor does jaundice save as an occasional, mild, transitory phenomenon Smith and O Flynn describe the liver histology in their case and state that the division into lobes and lobules was ill-defined especially at the periphery owing to invasion of the parenchyma by fine strands of connective tissue Under high power they found as striking features enlargement of the liver cells to three or four times their normal size with preservation of the nuclei in most of the cells, an empty appearance of certain individual cells and an increase of connective tissue in the portal spaces with a tendency for the liver cells to be separated into groups of from four to twenty cells by fine connective tissue strands

By appropriate staining methods they demonstrated the absence of fat and lipoids in the cells When the tissue is stained suitably after fixation with alcohol the presence of glycogen can be determined, but with other methods of fixation, such as formalin the glycogen tends to disappear

The chief functional pathology seems to be the inability of the body to utilize glycogen it seems to be fixed in the tissues where it accumulates Certain phenomena of general development and appearance will be described under Symptomatology, the clinical laboratory findings will be discussed in special section

The kidneys often are affected along with the liver but their enlargement, while marked, is of less extreme degree In some cases the heart seems to bear the brunt of the disease Antopol and his associates[4] describe a case in a 4½ months old child in which the heart weighed 85 grams and the ventricles were almost completely filled by the enlarged papillary muscles Even though the organs from this child were fixed in formalin for four weeks before being analyzed for glycogen the heart was found to contain 3 57 per cent the liver 3 5 per cent the kidneys 4 34 per cent and the lungs 0 32 per cent They state that deposits of glycogen may occur in the liver kidneys brain heart blood vessels muscles and organs of internal secretion They also raise the very interesting question as to whether many cases of so-called congenital idiopathic hypertrophy of the heart may not be unrecognized cases of von Gierke s disease This would not apply to the numerous cases studied pathologically

Von Gierke described atrophy of the suprarenals in his original case, and Smith and O Flynn reported marked pigmentation and hirsutism in their patient Other observers have found the adrenals normal

Symptomatology — We may recognize three major clinical types based on the organs chiefly affected though mixed types are frequent

1 *The Hepatic or Hepatorenal Type* (*Glycogenic Hepatomegaly*) This is the most frequent and striking type As in all types the onset is insidious in infancy or early childhood Subjective symptoms usually are insignificant or absent However Worster Drought s patient gave a history of epileptiform attacks and recurrent vomiting mixture of hepatic and cerebral types As a rule the child is taken to a physician because the parents have noticed a marked enlargement of the abdomen Examination shows this to be due to a huge liver The spleen is not enlarged though the left lobe of the liver has been mistaken for a spleen[7] There is no demonstrable ascites and other evidences of portal obstruction such as dilated veins in the abdominal wall are absent. So far as the writer knows edema of the legs has not been reported Jaundice has been described as a mild fleeting phenomenon but is exceptional and the absence of severe or persistent jaundice is an important diagnostic point

The general appearance of the patient is of interest There is usually some retardation and disproportion in bodily development The head is likely to be somewhat large in proportion to the undersized body The weight usually is fairly proportionate to the height but the body fat is unevenly distributed The cheeks are very full almost as if the child were blowing or whistling though the mouth and nose may be small The neck usually is fat and a double chin has been noted[8] The thorax is thick short and fat Pads of fat may occur in the flanks thighs suprapubic region knees elbows etc The buttocks however usually are small and contain less fat than normally and

the extremities are thin except for the pads mentioned above The muscles often are poorly developed, and there may be delay in learning to walk, disturbances of gait, difficulty in standing upright, etc, due perhaps in part to the poor muscular development and in part to cerebral involvement in some cases Normal muscular development has been reported Some pallor due to a moderate anemia is frequent, but rarely is it extreme Smith and O Flynn s exceptional case showed such marked general pigmentation of the skin that the patient "resembled a mulatto ' at the last and showed a profuse growth of hair on the head and trunk, while the limbs were covered with a fine down. Moderate degrees of mental retardation have been noted in some cases The kidneys may be considerably enlarged in this type, but the huge liver usually precludes the possibility of palpating them The disease is afebrile when uncomplicated Repeated epistaxis has been noted by several observers, and small hemorrhages in the skin have been described, as has hematemesis, but the last two phenomena are unusual An odor of acetone on the breath has been noted often, and this may persist over a long period and constitute a very suggestive symptom in the absence of the usual causes of ketosis

2 *Cardiac type* —The essential feature of this type is a marked enlargement of the heart without obvious cause in an infant or child Here, too, there is a striking lack of subjective symptoms though cyanosis and dyspnea are noted occasionally There may be associated enlargement of the kidneys

3 *Cerebral Type* —This is a rather poorly defined group in which mental retardation is likely to be especially marked Epileptiform attacks have been described, as noted above Antopol and his associates[8] go so far as to suggest that there is need for a general review of all poorly understood cerebral disturbances in children to determine if some may not be due to abnormal glycogen storage in the brain

In all types the general health seems little affected A history of the disease in two children of one family is rather frequent [10 11] The deaths that have occurred usually have been due to complicating infections notably pneumonia. Heart failure may, however, occur in the cardiac type.

Clinical Laboratory Findings —*Urine* A notable feature of the disease often occurs in the urine, viz the constant or nearly constant presence of acetone and diacetic acid without sugar or other abnormal urinary findings and without starvation excessive vomiting or other ordinary cause for ketosis. The *stool* shows nothing characteristic

Blood —A moderate anemia is often found, though this is not essential for diagnosis 3 000 000 red cells per cu mm with 50 per cent hemoglobin would represent a fairly typical blood picture in a well-developed case In uncomplicated cases the absolute white cell count usually is within normal limits A relative lymphocytosis is the rule but this is true of childhood

generally, so cannot be considered significant as practically all the cases reported have been in children Both direct and indirect van den Bergh tests have been found negative Liver function tests give results within normal limits The fasting blood sugar usually is somewhat low and in a glucose tolerance test there is a well marked delay in the rise of the blood sugar curve and some prolongation of it Warner[11] describes an unusually low fasting blood sugar (48 mg %) without hypoglycemic symptoms Lipemia has been noted in some cases[3]

The most important laboratory test of all is the reaction of the blood sugar curve to epinephrin This reaction taken in conjunction with the clinical picture is highly diagnostic Normally epinephrin quickly mobilizes glycogen in the liver and causes it to appear in a few minutes as additional glucose in the blood If after obtaining the fasting blood sugar value a small dose of epinephrin be injected subcutaneously the value either does not rise at all or rises much less than in the normal person

Many other laboratory studies have been made in this disease, but they have not proved of diagnostic value

Diagnosis — The important diagnostic features are the onset at an early age the presence of an enormous liver without chronic jaundice ascites or splenic enlargement and with little subjective disturbance a more or less characteristic disproportion of various parts of the body with an irregular distribution of subcutaneous fat a low fasting blood sugar with lack of normal response to epinephrin normal results from functional liver tests and a tendency to persistent ketosis with ketone bodies in the urine and an acetone odor to the breath without the usual causes of ketosis

Prognosis — This must be guarded Though most writers note that there seems to be little effect produced on the general health by the disease per se, yet a considerable proportion of the patients recorded have died of some intercurrent infection notably pneumonia in childhood or early life The writer has found no record of a case in a patient living to an advanced age Definite improvement with decrease in the size of the liver has been noted and Worster Drought s case at least seems to indicate that spontaneous recovery may occur[1, 2] This seems to be exceptional however and the usual course is one of great chronicity lasting from one to twenty years or more We may consider sudden heart failure as a particular hazard of the cardiac type The cerebral type is thus far too vague and poorly defined to permit of any special prognosis

Treatment — Nothing is known which modifies the course of the disease Some form of abdominal support might be worth trying in certain cases to lessen the dragging weight of the huge liver but marked compression of the abdomen should be avoided as the liver already crowds the other abdominal

the extremities are thin except for the pads mentioned above The muscles often are poorly developed, and there may be delay in learning to walk, disturbances of gait, difficulty in standing upright, etc, due perhaps in part to the poor muscular development and in part to cerebral involvement in some cases Normal muscular development has been reported Some pallor due to a moderate anemia is frequent, but rarely is it extreme Smith and O Flynn s exceptional case showed such marked general pigmentation of the skin that the patient 'resembled a mulatto at the last and showed a profuse growth of hair on the head and trunk while the limbs were covered with a fine down Moderate degrees of mental retardation have been noted in some cases The kidneys may be considerably enlarged in this type, but the huge liver usually precludes the possibility of palpating them The disease is afebrile when uncomplicated Repeated epistaxis has been noted by several observers, and small hemorrhages in the skin have been described, as has hematemesis, but the last two phenomena are unusual An odor of acetone on the breath has been noted often and this may persist over a long period and constitute a very suggestive symptom in the absence of the usual causes of ketosis

2 *Cardiac type* —The essential feature of this type is a marked enlargement of the heart without obvious cause in an infant or child Here, too, there is a striking lack of subjective symptoms, though cyano is and dyspnea are noted occasionally There may be associated enlargement of the kidneys

3 *Cerebral Type* — This is a rather poorly defined group in which mental retardation is likely to be especially marked Epileptiform attacks have been described as noted above Antopol and his associates[8] go so far as to suggest that there is need for a general review of all poorly understood cerebral disturbances in children to determine if some may not be due to abnormal glycogen storage in the brain

In all types the general health seems little affected A history of the disease in two children of one family is rather frequent[7, 10, 11] The deaths that have occurred usually have been due to complicating infections, notably pneumonia Heart failure may however, occur in the cardiac type

Clinical Laboratory Findings —*Urine* A notable feature of the disease often occurs in the urine viz the constant or nearly constant presence of acetone and diacetic acid without sugar or other abnormal urinary findings and without starvation excessive vomiting or other ordinary cause for ketosis. The *stool* shows nothing characteristic

Blood —A moderate anemia is often found though this is not essential for diagnosis 3 000 000 red cells per cu mm with 50 per cent hemoglobin would represent a fairly typical blood picture in a well-developed case In uncomplicated cases the absolute white cell count usually is within normal limits A relative lymphocytosis is the rule, but this is true of childhood

History — The condition was established as a clinical entity in 1893 by Dejerine and Sottas[1] They state however, that in 1889 Combault and Mallet reported what was probably a case of this disease as an unusual form of tabes.

Etiology — This is unknown A familial incidence has been observed in some cases but is not essential The disease frequently begins in childhood but in recent years an increasing number of cases beginning in adult life have been reported A case has been reported in a negro Some of the patients of record especially among the earlier accounts have had syphilis but many have not and Dejerine and Sottas considered the syphilis as coincidental rather than causative

Pathology — The essential feature is a marked enlargement of the nerves of the extremities On microscopic examination this is seen to consist chiefly of a great thickening of the sheaths of Schwann hence the terms schwannitis and schwannosis Both perineurium and endoneurium are increased in amount The sheaths of Schwann are not only thickened but show an increased number of nuclei looking according to Wolf and hi associates like onion bulbs in a cross section of the nerve These authors found the myelin sheaths reduced in number Harris and Newcomb[3] report finding a sciatic nerve $1\frac{1}{2}$ inches in diameter and when they demonstrated it a pathologist humor ously suggested that they had brought a bullock s sciatic nerve to display Occasionally a nerve may show nodular or fusiform enlargements[4] Almost always the four extremities show muscular atrophy most marked in their distal portions

Symptomatology — This is very varied The onset as stated above is often in childhood but may be in adult life Muscular weakness is practically always present especially in the hands feet forearms and legs Atrophy of the muscles is found almost always and this involves especially the most distal parts of the extremities and diminishes as the trunk is approached The hands may present a typical main en griffe appearance and the feet may show a picture resembling an equinus or equinovarus deformity[1] Fibrillary contrac tions often are noted in the muscles The weakness usually is in proportion to the atrophy though Wolf and his associates[2] cite a patient of Schaller s who showed no atrophy despite muscular weakness for seven years The tendon reflexes are absent and electrical examination often shows the reaction of de generation Shooting pains in the extremities are frequent Other sensory disturbances are extremely variable ranging from mere slight numbness of the finger tips to a complete stocking and glove type of anesthesia and analgesia in all four limbs Trophic disturbances of the skin have not been reported Kyphoscoliosis was reported in a number of the early cases but other cases have not shown this A few of the cases reported have shown Argyll Robertson pupils and even a positive Wassermann reaction Despite the great authority

viscera severely Laxatives may be required to overcome intestinal stasis due to pressure from the liver Whether drugs can act effectively on a myocardium containing an enormous accumulation of glycogen is an interesting question but there can be no harm in trying the usual remedies in the presence of heart failure

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Progressive Hypertrophic Polyneuritis

Synonyms — Dejerine Sottas disease, interstitial hypertrophic polyneuritis, progressive hypertrophic schwannitis progressive hypertrophic schwannosis

Definition — A chronic progressive polyneuritis of the extremities characterized by marked enlargement of the nerves involved with a variety of motor and sensory symptoms, notably muscular weakness, atrophy and shooting pains

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Ileus with Transient Renal Insufficiency

Synonym —Wakefield Mayo Bargen enterorenal syndrome

Definition —A syndrome in elderly persons characterized by symptoms of colonic obstruction without gross anatomic lesions as a cause associated with symptoms of renal insufficiency including albuminuria a lowered urinary output a high concentration of blood urea and blood chlorides and various other disturbances

History —So far as the writer has been able to learn the paper by Wakefield C W Mayo and Bargen[1] which appeared in 1935 is the only article on the subject under this title thus far in the literature

Etiology —Nothing is known of the etiology of this disease beyond the facts that it seems to occur chiefly in elderly males that all the cases thus far observed have exhibited some degree of arteriosclerosis that in two patients operated upon organic obstruction was definitely excluded and that renal calculus does not seem to be a factor Gall bladder disease was found in the two patients operated on but Wakefield and his associates regard this as probably coincidental and advance a tentative theory that the syndrome is due to imultaneous circulatory disturbances in the kidneys and intestines probably as a result of the arteriosclerosis Of the ten cases nine were in males and one in a female The youngest patient was 54 years old the oldest 84 and the average age was 67 1 years

Pathology —Only one patient died of the syndrome and one other a man aged 8 who seemed to be recovering suffered a fatal attack of what was considered coronary disease No necropsy has been reported thus far Laparotomy was performed in two cases Anatomic intestinal obstruction was absent. In one patient the ascending and transverse colon were dilated in the other the lower ileum and ascending colon

Symptomatology —Some patients gave a history of chronic constipation All showed obstinate constipation for several days practically unaffected by enemas or purgatives with marked abdominal distention but no palpable masses In some cases abdominal tenderness was noted Two patients com

of Dejerine, the writer is inclined to view with suspicion a diagnosis of progressive hypertrophic neuritis in a patient presenting characteristic signs of neurosyphilis Other findings reported in individual cases include ataxia, intention tremor, scanning speech, nystagmus, etc [2]

Diagnosis — In many of the cases reported this has been made only at necropsy When superficial nerve trunks are visibly or palpably enlarged, the diagnosis may be tentatively made, if the picture is in other ways typical of a prolonged polyneuritis and the common causes of that condition are absent Pronounced sensory symptoms should exclude *progressive spinal muscular atrophy* but where these are absent the differential diagnosis might be very difficult or impossible unless definite enlargement of the nerves could be seen or felt The absence of tendon reflexes and of sphincter disturbances tend to exclude *disseminated sclerosis* In the presence of Argyll Robertson pupils or positive serologic evidence of syphilis the author would consider the case one of *neurosyphilis* rather than of the disease under consideration An onset in childhood and a familial incidence somewhat favor progressive hypertrophic neuritis Excision and microscopic examination of a portion of an enlarged nerve would establish the diagnosis conclusively

Prognosis — Typically the disease is extremely chronic Several middle aged persons with the disease have reported its onset in childhood Harris and Newcomb's patient was unique in having recurrent attacks of what appeared to be polyneuritic paralysis over a period of six years with complete recovery between attacks The last attack however, was progressive over 12 months with muscle wasting and foot drop and in the end there were attacks of choking severe dyspnea and finally fatal paralysis of the diaphragm These authors found degeneration in the roots of the phrenic and vagus nerves and raise a question as to the identity of the condition with the usual type of the disease They cite Natras as describing a patient who suffered three attacks of polyneuritis at intervals of several years in whom the nerve trunks seemed palpably enlarged and who apparently recovered Certainly these are exceptional cases The usual picture is that of slow steady progression with symmetrical crippling of the four extremities, especially in their distal portions but with little effect on longevity

Treatment — There is no effective treatment Pain should be relieved, preferably by physical therapy when practicable Theoretically at least, the diet should be rich in vitamin B

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Jan. 1 1936

Hereditary Arthrodysplasia with Dystrophy of the Nails

Definition —A hereditary condition characterized by developmental defects in certain joints and in the nails

History —In 1933 Turner of Atlanta[1] described this condition and collected data from two families in which among a total of 79 persons 35 were victims of it In 1935 Aschner of Vienna[2] discussed the mechanism of inheritance of the condition in some detail and collected a number of cases from the European literature including a report of six cases in one family by Trauner and Rieger in 1925[3]

Etiology —This is unknown beyond the fact that it is a hereditary anomaly Hereditary dystrophy of the nails alone or in combination with a number of abnormalities of other ectodermal structures such as the skin hair teeth etc is not unusual and the dermatologic literature contains numerous reports of such Dystrophy of the nails associated with mental defect also is well known The striking association of joint involvement as a constant factor in certain families such as occurs in the condition under discussion moved Aschner[2] to seek the reason therefor and by way of a solution of this question she postulated a very close proximity in the same chromosome of the genes representing certain of the parts affected as e g the nails and patellæ plus a constitutional inferiority of the joints There is no sex linkage in the heredity

Pathology —This is grossly obvious from the physical signs and roentgenologic findings

Symptomatology —This varies in different individuals according to the degree and location of the parts affected All have shown a dystrophy of the nails varying often in the same individual from a simple thinning to a total absence of the nail In some cases the thumbs showed the most advanced dystrophy of the nails and the little fingers the least Both fingers and toes may be affected

The joints chiefly involved have been the knees elbows and shoulders Subjective symptoms when present have been due to poor function of the joints Thus with involvement of the knees frequent falling when running has been complained of and with elbow involvement inability to completely extend the forearm has been noted

plained of continuous abdominal pain for many months All showed evidences of arteriosclerosis which was of moderate degree in eight and advanced in two Only one showed any fever (101° F) A dry tongue and skin were noted in some cases as was hiccup Several patients showed a slight elevation of pulse rate the maximum reported being 1 0 Half the patients complained of occasional nausea and vomiting One had cramps in the legs another showed musical rales in the chest, but these phenomena probably should be considered as merely coincidental Four had gastrointestinal roentgenological studies reported, all of which were negative Edema was noted as absent in two cases and no note was made of its presence in any case One patient had pupils which were sluggish to light but had normal reflexes ' One showed a ventral hernia and bilateral inguinal hernia with no evidence of incarceration The blood pressure did not appear to be significant, for in the various cases the systolic varied from 105 to 225 and the diastolic from 65 to 130 Over half the patients showed a pressure within reasonably normal limits.

Clinical Laboratory Findings — Urine — All patients showed a decreased urinary output of varying degree the most marked less than 500 c.c. in 4 hours All showed slight to moderate albuminuria, all but one some pus, three showed erythrocytes No mention is made of the presence or absence of casts.

Blood — The minimum hemoglobin reported was 66 per cent, the maximum 96 per cent the average in the ten cases being 79 2 per cent Red and white cell and differential counts are not reported The blood urea was markedly elevated ranging from 52 mg per 100 c c of whole blood to 1 6 mg The blood chlorides were also high running from 530 mg per 100 c c of plasma to 691 mg The CO_2 combining power of the plasma was normal

Diagnosis — This depends on a history of obstinate, practically absolute, constipation for some days, plus a distended abdomen without any palpable mass with or without pain nausea and vomiting without shock and with definite signs of renal insufficiency including albuminuria, high blood urea and blood chloride levels and a normal CO_2 combining power of the plasma.

Prognosis — In the ten cases reported from the Mayo Clinic two died but one of these deaths probably was due to complicating coronary disease Excluding this we may consider the mortality of the syndrome in these cases to be 10 per cent With appropriate treatment convalescence usually is well established within a week

Treatment — This is non surgical and consists of abundant fluid, 3 000 c c or more, by mouth with rectal or intravenous administration if needed, warm rectal irrigations with physiologic salt solution twice daily and hot stupes to the abdomen A bland diet is indicated Improvement usually is noted promptly, and in most of the cases reported the symptoms cleared up and the laboratory findings returned to normal within a week or less

History — According to Muir[1] Greig published a report of this condition in 1924 and coined the name hypertelorism which means separated too far apart and refers to the abnormally great distance between the eyes Greig obtained the skulls of his patients The condition as described by him was bilateral Muir[1] also states that Fridolin described a unilateral form in 1890 but made no effort to explain the nature of the developmental defect simply reporting it as an abnormal skull [3]

Etiology and Pathology — Greig and Muir agree that the essential change is an abnormal evolution of that part of the sphenoid bone which is developed from cartilage There is lack of growth in the region of the pterion so that the occiput does not develop backwards and this throws the pressure of the growing brain forwards Greig states that the initial defect is fully developed in the embryo by the third month and that the ethmoid becomes distorted by pressure with broadening of the horizontal plates and absence of the crista galli and labyrinth of the ethmoid A typical fetal facies is preserved and large intersutural bones may develop at the pterion and asterion

Symptomatology — While associated anomalies have been described the abnormal signs are typically limited to the head The most striking sign is the *extraordinary width of the space between the eyes* This may or may not be noticed at birth but it becomes increasingly obvious as the head grows Mental defect may be associated Muir s patient was brought to him at the age of 12 months because of inability to sit up The peculiar head was obvious at a glance Muir[1] describes his patient as having the eyes very far apart the bridge of the nose flattened and the tip of the nose turned up so that the nostrils looked forwards The eyes though large and prominent seemed too small for the enormous sockets On both sides the lower edge of the zygoma extended to the alveolar margin The palate was narrow and high The general shape of the head was square The anterior fontanelle was wide open the posterior just palpable The occiput was flattened and the neck broadened transversely The patient s back was hirsute

Cockayne[4] reports as associated conditions in various cases prominent ears short square fingers and toes webbed fingers and various types of hernia but these findings are not essential features of hypertelorism

Lightwood and Sheldon[5] report a unilateral case with an associated torticollis which they consider due to the external deviation of the right eye Montford[6] reports a case of hereditary hypertelorism without mental deficiency in a child aged 2 years and 1 month in whom the distance between the inner canthi of the eyes was 40 mm (1 6 inches) The child s mother was hypertelonic intelligent and emotional. Whitwell[7] reports a case associated with brittle dry rudimentary nails

Diagnosis — This is obvious on inspection in the typical bilateral case.

Physical and roentgenological examination have shown various defects in joint structures, including the following 1 Absent or rudimentary patellæ, causing the knees to appear flat when extended and angular when flexed Along with this, the upper ends of the fibulæ have been found small and poorly developed 2 Small rudimentary heads of the radii are the rule, and congenital dislocation of a radius is not infrequent 3 Small scapulæ with notably small acromial processes which do not come forward above the heads of the humeri prominent acromial ends of the clavicles with the glenoid cavities seeming to be in front of them, making the rather underdeveloped heads of the humeri prominent In one case Turner[1] noted a thickening of the lower three inches of a humerus with a "hump" on its posterior surface in that region. One of his patients could hyperextend all the fingers in all their joints, and this same patient showed thick ankles with the internal malleoli larger than the external, contrary to the usual rule

Clinically no abnormalities of the hips and pelvis have been reported, but Turner[1] reported that roentgenologically the necks of the femora were more nearly in line with the shafts than is usually the case

Diagnosis — This is obvious on inspection, palpation and roentgenologic examination

Prognosis — The condition is permanent and incurable

Treatment — When joint function is significantly impaired, orthopedic correction should be considered

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Hypertelorism

Definition — A congenital anomaly of the skull affecting the sphenoid bone particularly, resulting in a characteristic appearance of the head the most striking feature of which is the extraordinarily great width between the eyes

himself for a minor ear complaint From birth he had seemed rather weak and thin though he walked at nine months Nothing remarkable was noted until his fourteenth year, when his weakness increased rapidly especially in the lower extremities so that he had to use canes and a year later crutches to walk The bones bent at every attempt to stand or walk and he had suffered 17 or 18 fractures of his lower extremities all told due to falls or blows He did not sustain any fractures in his upper extremities but his forearms became bent

About four years after the onset of the bone changes he noted a gradually increasing stiffness of the joints of the upper extremities especially the elbows There was no pain unless he made forcible attempts to move the stiff joints The stiffness gradually involved almost all the larger joints of the body including the temporomandibular and vertebral articulations but the fingers and toes were spared

In the early years of his disease no muscular involvement was noted but about five years before Bruck saw him he developed atrophy of various muscle groups accompanied by deep boring pains His extremities wasted to an extreme degree and became so bent and bowed that he was confined to a wheel chair His teeth became painlessly carious and he began to have difficulty in breathing and to sweat profusely Despite his extreme crippling he kept cheerful and even humorous about his condition and ate and slept well

Physical examination showed a monstrous deformity Bruck writes He sits as though crouching or squatting in his wheel chair The knees are sharply drawn upward against his chest his rather massively developed head seems somewhat sunk into the shoulders The legs are so bent that the size of the body as a whole seems considerably lessened Weighing 64 lbs the body measures about 4 feet 8 inches in length The extremities are so thin that on transillumination opaque objects can be seen behind them The bones appear flattened and covered merely by thin almost transparent skin Both thighs are bent almost at right angles Above the right knee is an area that is tender on light pressure where his most recent fracture occurred a year previously from an accident The tibiæ are bowed anteroposteriorly with the convexity anterior the right tibia being only 1 cm wide and the left 1 3 cm The fibulæ are evident in their lower portions There was marked limitation of motion of the hips knees and right foot A striking disproportion was noted between the two feet on forcible but uneven straightening of the feet the right sole was 14 cm long the left 19 cm The forearms were symmetrically bowed but showed no atrophy rather there seemed to be some hypertrophic thickening Both elbows and the right wrist were immobilized by exostoses The shoulders could be moved but slightly the left less than the right The temporomandibular joints were limited in movement by bony new growth

In a unilateral case it may be necessary to make measurements from the mid line to the inner canthi of the eyes, or to use a cardboard screen or like device so that the two halves of the face may be inspected separately

Prognosis — The condition obviously is permanent When mental defect is associated the prognosis as to life is that associated with the degree of deficiency When the brain is normal, there is no reason why life expectancy should be shortened as evidenced by the mother of Montford's patient mentioned above

Treatment — There is naturally no effective treatment In an intelligent patient with visual defects an ophthalmologist should be consulted and if remediable associated conditions such as torticollis are present, suitable treatment should be directed towards them

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Jan 1 1936

BRUCK'S DISEASE

Definition — A progressive disease of the locomotor system giving rise to extensive absorption of bone multiple fractures, ankylosis of joints and muscular atrophy with resultant gross bodily deformity

History — In 1897 Alfred Bruck of Berlin gave the only report of this disease that has appeared in medical literature up to the present time so far as the writer knows

Etiology — This is unknown Syphilis is not a factor

Pathology — No necropsy report is available so our knowledge is limited to information gained from examination of the living patient. This will be discussed under Symptomatology

Symptomatology — As only one case has been reported, it is unsafe to attempt any generalizations regarding the clinical picture The essential features observed by Bruck were as follows The patient was a man of 31, who presented

Prognosis and Treatment — The disease is progressive and incurable It is presumable that the gross thoracic deformity of the end stages may shorten life somewhat by causing respiratory embarassment Treatment is symptomatic only Orthopedic devices may be helpful in certain cases

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March 1 1937

Hereditary Enlargement of the Parietal Foramina

Definition — A hereditary familial condition in which approximately circular symmetrical defects occur in the posterior portions of the two parietal bones near the sagittal suture When the defects are large the two may merge with the formation of a bridge defect joining the two circular ones

History — Skulls showing the characteristic defects have long been known to anthropologists and anatomists One such skull was discovered in a pre white Indian burial ground in Palo Alto California (Ales Hrdlicka quoted by Pepper and Pendergrass) In 1891 Greig reported a case in a soldier feigning symptoms to escape military duties who admitted after discharge from the service that he had suffered no discomfort from his condition that it had been present all his life and that others in his family had the same defect This was probably the first case diagnosed and reported during life One family by the name of Catlin had so many cases in several generations that they called the defect the Catlin mark

Etiology — This is unknown Syphilis osteomyelitis tuberculosis the Schuller Christian syndrome etc are not factors Both sexes may be affected and may transmit the defect

Pathology — The main features are given in the definition The two openings resemble the holes in a bowling ball Usually they are about equal in size and may be smaller than a dime or as large as a half dollar The edges are smooth and there is no noticeable thickening of the skull An associated defect in the occipital bone has been described The embryology of the condition is discussed exhaustively by Cohn

Diagnosis — There being no subjective symptoms this depends entirely on physical and roentgenologic examination The openings may be felt by light palpation In one case pressure on the overlying scalp was reported as causing pain in the head and flashes of light in the eyes The important thing is to recognize the condition as a harmless defect rather than as a manifestation of

The head could be turned freely to the left but only slightly to the right, and other neck movements were limited" As stated above, the fingers and toes were spared The chest was contracted laterally and bent towards the right with a corresponding scoliosis The crest of the left ilium was anterior to the lower ribs and that of the right posterior The sternum was markedly displaced forward and showed many lump-like processes The right pectoral muscles functioned the left did not No visceral symptoms were noted other than occasional dyspnea, presumably due to the thoracic deformity The urine was negative

Roentgenology had scarcely been born, but pictures were made by means of x ray singularly adapted for determining bone lesions" The right wrist showed bony growth between the individual carpal bones and bones of the fore arm also bony ankylosis of the elbow was found 'Striking is the bending of the flat tibia and the almost serpentine curving of the fibula Particularly do I wish to point out the dark cross piece that appears to unite the bones Bruck could not explain the significance of this

He concludes as follows "In retro pect I wish to venture the opinion that we are dealing with a monstrous deformity by which high grade absorption of bone leads to immobilization of most of the joints Prof Virchow, who had the kindness to visit this patient on two occasions labelled the process 'a wasting disease of bone which during the years of its presence has through its spread brought the skeleton to a complete atrophy so that only a meager residue of earlier substance remains and so far as his judgment is concerned, the case remains at present one of the most interesting of pathological specimens and a convincing example of human adaptability"

Diagnosis — Because of the gross deformity and bowing of the bones *osteitis deformans* (*Paget s disease*) may superficially resemble Bruck s dis as However osteitis deformans characteristically appears later in life, the bones are grossly enlarged rather than thinned and flattened pain is an early symptom ankylosis of the joints is not marked, muscular atrophy exists only in proportion to the disuse of the muscles and spontaneous fractures, while they may occur, form a much less striking feature of the disease *Osteomalacia* shows a softening of the bones is painful throughout its course and occurs usually in the female especially during pregnancy

Osteopsathyrosis (*osteogenesis imperfecta*) may show a marked resemblance to Bruck's disease for multiple fractures are the rule gross deformity develops widespread muscular atrophy may occur, and marked sweating has been described Ankylosis is rare, however, in osteopsathyrosis the cranium shows an almost complete lack of calcification, pain is not a prominent feature of the disease at any time, and the condition usually is manifest at birth or soon thereafter though an adult form has been described

Prognosis and Treatment — The disease is progressive and incurable It is presumable that the gross thoracic deformity of the end stages may shorten life somewhat by causing respiratory embarassment Treatment is symptomatic only Orthopedic devices may be helpful in certain cases

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Diagnosis — There being no subjective symptoms this depends entirely on physical and roentgenologic examination The openings may be felt by light palpation In one case pressure on the overlying scalp was reported as causing pain in the head and flashes of light in the eyes The important thing is to recognize the condition as a harmless defect rather than as a manifestation of

The head could be turned freely to the left but only slightly to the right, and other neck movements were limited" As stated above, the fingers and toes were spared The chest was contracted laterally and bent towards the right with a corresponding scoliosis The crest of the left ilium was anterior to the lower ribs, and that of the right posterior The sternum was markedly displaced forward and showed many lump-like processes The right pectoral muscles functioned, the left did not No visceral symptoms were noted other than occasional dyspnea presumably due to the thoracic deformity The urine was negative

Roentgenology had scarcely been born but pictures were made by means of x ray singularly adapted for determining bone lesions The right wrist showed bony growth between the individual carpal bones and bones of the fore arm also bony ankylosis of the elbow was found Striking is the bending of the flat tibia and the almost serpentine curving of the fibula Particularly do I wish to point out the dark cross piece that appears to unite the bones. Bruck could not explain the significance of this

He concludes as follows 'In retrospect I wish to venture the opinion that we are dealing with a monstrous deformity by which high grade absorption of bone leads to immobilization of most of the joints Prof Virchow, who had the kindness to visit this patient on two occasions labelled the process 'a wasting disease of bone which during the years of its presence has through its spread brought the skeleton to a complete atrophy so that only a meager residue of earlier substance remains and so far as his judgment is concerned, the case remains at present one of the most interesting of pathological specimens and a convincing example of human adaptability"

Diagnosis — Because of the gross deformity and bowing of the bones, *osteitis deformans* (*Paget's disease*) may superficially resemble Bruck's disease However osteitis deformans characteristically appears later in life, the bones are grossly enlarged rather than thinned and flattened pain is an early symptom ankylosis of the joints is not marked, muscular atrophy exists only in proportion to the disuse of the muscles and spontaneous fractures while they may occur form a much less striking feature of the disease *Osteomalacia* shows a softening of the bones is painful throughout its course and occurs usually in the female especially during pregnancy

Osteopsathyrosis (*osteogenesis imperfecta*) may show a marked resemblance to Bruck's disease for multiple fractures are the rule, gross deformity develops widespread muscular atrophy may occur and marked sweating has been described Ankylosis is rare, however in osteopsathyrosis the cranium shows an almost complete lack of calcification pain is not a prominent feature of the disease at any time, and the condition usually is manifest at birth or soon thereafter though an adult form has been described

Etiology and Pathology — The real cause is unknown The defect is one of prenatal development and often affects several persons in a family Both sexes may be affected and transmit the condition A number of isolated non familial cases have been observed.

Symptomatology — Usually there are no subjective symptoms other than the consciousness of the defects. Leopold and Castrovinci point out as the chief features an aplasia more or less marked of one or both clavicles an exaggerated development of the transverse diameter of the cranium a delay in ossification of the fontanels and hereditary transmission The clavicular deformity is indispensable Any or all of the other features may be absent. Other phenomena may include prominent frontal and parietal bosses grooved cranial sutures especially the sagittal a high arched palate delayed eruption of or irregular teeth pointed terminal phalanges of fingers increased length of the proximal phalanges of the big toes abnormalities of the scapulæ deformities of the pelvis a short face concave nose large lower lip prognathous mandible peculiarities in the shape of the sternum scoliosis lordosis kyphosis prominence of the transverse processes of a cervical vertebra genu valgum club feet curvatures of the long bones flat chest pigeon breast etc Many cases are undersized and poorly developed in general. A few have shown substandard intelligence but this is unusual

The clavicular defect may range from a fibrous band joining the two ends of one clavicle to total absence of both clavicles Both are affected symmetrically more often than one alone Neuritis with muscular atrophy in one arm due to a mobile clavicular fragment has been reported Removal of the fragment cleared up the symptoms. A very striking physical sign dependent on the unusual mobility of the shoulders may be elicited by pressing the shoulders forwards and towards each other till they meet in front of the chest. The patients usually are active and their general health good

Diagnosis Prognosis and Treatment — Diagnosis depends on physical and roentgenologic examination Occasionally when both ends of a clavicle are present the differential diagnosis from fracture may assume medicolegal importance Fractures of the clavicle from birth trauma practically always unite are almost never bilaterally symmetrical and usually are not associated with cranial or other defects. Traumatic fractures occurring later in life show excess callus if they fail to unite as well as the other differential points noted with regard to birth fractures

The condition while permanent usually does not affect life or health. A case has been recorded in a o year old man

The clavicular defect does not require treatment unless a fragment causes a pressure neuritis when it should be removed surgically Certain associated defects such as spinal curvature when present may require orthopedic correction.

syphilis osteomyelitis the Schüller Christian syndrome, or other serious condition The symmetrical, sharp clear cut, nearly circular openings close to the midline just anterior to the lambdoidal suture, occasionally with a bridge defect connecting the two rarely with an associated defect in the development of the occipital bone the cranium being otherwise normal roentgenographically in the absence of exophthalmos and diabetes insipidus and with negative laboratory tests for syphilis should prevent confusion with other familiar conditions presenting pathological changes in the skull

Prognosis and Treatment — The defect is permanent and treatment is unnecessary

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Cleidocranial Dysostosis

Definition — A developmental defect often familial characterized by partial or total absence of one or both clavicles associated with various cranial anomalies Many other associated defects have been described in individual cases A pure congenital absence of the clavicles without cranial involvement occurs rarely

History — Absence of the clavicles often associated with other gross defects such as absence of the sternum and costal cartilages etc was noted occasionally by anatomists and pathologists for more than a century before Marie and Sainton in 1897 published the first description of the condition in two living patients, a father and son and called it 'hereditary hydrocephalus with a defect in development of the cranium and brain Since that time over 100 cases have been reported in the literature Leri and Lievre believe that the condition would be considered less rare if we developed the habit of looking for anomalies routinely

certain and the vision poor owing to muscular relaxation depending on malformation of the skull Otherwise subjective symptoms are absent

The *diagnosis* is obvious on inspection in a well marked case

Prognosis and Treatment — The condition is permanent and there is no treatment.

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March 5 1937

ACROCEPHALOSYNDACTYLISM AND ALLIED CONDITIONS

Synonyms — Acrocephalosyndactyly acrocephaly with syndactyly oxycephaly with syndactyly acrosphenosyndactyly tower head with webbed fingers and toes Apert s syndrome

Definition — Acrocephalosyndactylism is a condition characterized by an abnormally high pointed top of the head the skull having a vertical index above 77 (acrocephaly) associated with webbing partial or complete of the fingers and toes (syndactylism) Acrocephaly may occur alone as may syndactylism but their association in the same individual is sufficiently frequent to constitute a well recognized syndrome Other defects of development may be associated with either or both conditions

History — Unusually tall pointed heads have been known for a long time as has webbing of the fingers and toes According to Ruh Troquart in 1886 first described the combined syndrome A few other reports appeared from 1886 to 1905 but in 1906 Apert gave the classic description that has caused his name to be attached to the syndrome In 1920 Park and Powers published the most exhaustive discussion of the subject to date

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Craniofacial Dysostosis

Synonyms — Crouzon s disease hereditary craniofacial dysostosis.

Definition — A malformation affecting the bones of the cranium and face characterized by an abnormally prominent frontal bone exophthalmos hooked nose heavy lower lip prognathous mandible and high arched palate

History — In 1912 Crouzon reported the condition calling it hereditary craniofacial dysostosis In 1926 Comby reported a case without involvement of other members of the patient s family Several reports have appeared in the literature since including both familial and isolated cases

The *etiology* is unknown Either sex may be affected or transmit the condition

Pathology and Symptomatology — The chief features are given in the definition The degree of malformation varies greatly ranging from a slight exaggeration of normal features to a gross deformity in which the forehead rises to a high peak and the rest of the "top" of the head slopes acutely downwards to the occiput with the other salient features of the condition similarly exaggerated to a grotesque degree In some cases the ocular movements are un

drome and certain other anomalies Crouzon has pointed out that syndactyly is only one of many malformations associated with acrocephaly and other cranial deformities There are mixed types between craniofacial dysostosis and acrocephalosyndactylism Apert discussing Crozon s paper drew an analogy citing two types of fancy goldfish the telescope type which he compared to acrocephaly, and the fancy tailed and finned types which he considered analogous to syndactyly A combination of the two types has been developed comparable to acrocephalosyndactylism Apert regards his syndrome and craniofacial dysostosis as different degrees of the same hereditary mutations

Chotzen reported an extraordinary family in which the father had acrocephalosyndactyly one son had craniofacial dysostosis and another son had hypertelorism Roch reported a case of acrocephalosyndactyly in a man with heredosyphilis The two conditions were presumably coincidental as syphilis is usually absent

Diagnosis Prognosis and Treatment —The diagnosis is made by inspection Mild grades of the condition do not impair health In severe cases a rise in intracranial pressure may develop with headache loss of vision and death

With an excess in intracranial pressure decompression is indicated In mild cases dehydration by restriction of fluids according to Temple Fay s method might be tried but usually surgical decompression will be required and this should not be delayed in the presence of beginning loss of vision Lumbar puncture is dangerous as in brain tumor In selected cases surgery may be able to relieve in part at least the deformity and disability due to the syndactylism and the patient should be given the benefit of expert surgical opinion as to the advisability of such operation

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Etiology — The condition is a developmental anomaly, but we do not know the mechanism of its production Familial cases have been recorded, but the majority have not shown any such incidence The reason for the association of the two bizarre conditions is unknown but it seems to occur too frequently to be ascribable solely to the laws of chance

Pathology and Symptomatology — The most essential features are a cranium that is high in front and flattened behind with webbing of the fingers and toes A great number of occasional associated malformations may occur but are more or less incidental

Carpenter has given a very striking description of an extreme case in a boy five weeks old in which the head viewed from in front showed an outline suggesting an ace of diamonds the upper and lower points being the top of the cranium and the lateral angles gaps in the skull where the brain was in close contact with the overlying soft parts Two knobs, "like rudimentary horns of a young calf were on the top of the skull The eyes protruded in a frog like manner, the eyeballs being kept in position merely by the lids They could be dislocated from the orbits readily so that they would hang suspended by their muscle and nerve attachments The bridge of the nose was depressed so that the nostrils looked forwards Viewed from the side the face and forehead sloped back in a straight line from the tip of the chin to the top of the skull The head was flattened posteriorly there being no external occipital protuberance There was extensive webbing of the fingers and toes extending to the base of the nails There were six toes on each foot, all directed inwards, and small epigastric and umbilical hernias Two deceased sisters of the patient had similar deformities The parents were healthy

Most cases are less extreme than Carpenter s A vertical face, rather than sloping is common Gaps in the skull are rare Exophthalmos is frequent with oxycephaly as is optic neuritis with resulting loss of vision of varying degree Enlarged veins in the scalp have been noted, as has partial deafness The roofs of the orbits may be tilted downwards The temporozygomatic regions may or may not bulge laterally The palate usually is highly arched The syndactylism may be practically complete, involving all the fingers and toes, or of any lesser degree, involving part or all of the digits Polydactylism with webbing may occur as may fusion of the nails One case was reported with six toes on one foot but only four nails Mental deficiency has been noted especially in extreme cases but usually the mind is normal Severe cases may develop signs of increased intracranial pressure Simon, Ramos and Eldridge reported two cases of oxycephaly without syndactylism showing a decrease in blood calcium with what they called the classic triad ', tower head, exophthalmos and optic atrophy with blindness

A very interesting question arises as to the relation between Apert s syn

drome and certain other anomalies Crouzon has pointed out that syndactyly is only one of many malformations associated with acrocephaly and other cranial deformities There are mixed types between craniofacial dysostosis and acrocephalosyndactylism Apert, discussing Crozon s paper drew an analogy citing two types of fancy goldfish the telescope type which he compared to acrocephaly and the fancy tailed and finned types which he considered analogous to syndactyly A combination of the two types has been developed comparable to acrocephalosyndactylism Apert regards his syndrome and craniofacial dysostosis as different degrees of the same hereditary mutations

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Craniofacial Amphiarthrosis

Definition — A defect in ossification of the facial bones of such a character that the face can be moved as a unit on the cranium, giving the appearance of a face articulated with the cranium

History and General Discussion — In 1929 Leri and Lebourg demonstrated the case of a 13 year old girl with a condition previously undescribed in medical literature She was underdeveloped in general but the peculiar feature of her case was the fact that her face apparently could be moved on her cranium If her cranium was fixed in some position, and the examiner s finger placed in her mouth, her whole face could be moved as a unit on the cranium by the finger, as if the two were articulated Her blood calcium was normal

A few months later in the same year the authors demonstrated a second case in a boy aged 22 months They consider the condition due to an arrest in the development of ossification of the facial bones

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March 1 193

GILLES DE LA TOURETTE S DISEASE

Synonyms — Generalized convulsive tic screaming tic with echolalia and coprolalia tic general *maladie des tics des degeneres impulsive tic psychic tic*

Definition — A dramatic syndrome characterized by sudden explosions of widespread muscular jerkings including grimaces jerking of the head extremities or trunk sometimes involving almost all the skeletal muscles associated with explosive noises or words sometimes the repeating of words spoken in the patient s presence (echolalia) or sometimes the use of obscene words (coprolalia)

History — In 1885 Gilles de la Tourette published two accounts of this condition Literature on the subject is scanty in recent medical periodicals but a number of modern text books discuss it

Etiology — *This is unknown A neuropathic heredity usually is present* Familial cases have been noted Griffith and Mitchell consider the condition more akin to hysteria and psychasthenia than to habit spasm Kauner has described a case the symptoms of which began two weeks after an operation for tonsils and adenoids that was performed without an anesthetic on a patient nine years old A discussion of the etiology of tics in general may be found in Vol VII Chapt II of this work

Pathology — No structural changes have been found in the nervous system which account for the condition

Symptoms — The onset of symptoms usually occurs between the ages of nine and fifteen The movements are likely to start in the face and spread over a wide area *the whole body at times appearing to be involved* Grimaces jumpings spasmodic jerkings etc appear suddenly without warning The explosive sounds and words even when the latter are obscene are emitted without reference to any proprieties of situation Movements suggestive of tap dancing or shadow boxing have been described The patient may count automatically or make hissing sounds The attacks are said to last from one to four seconds without disturbance of consciousness and recur after varying intervals If a patient who is talking is seized with an attack in the middle of a sentence he is apt to resume the sentence quietly where he left off on the subsidence of the attack as if nothing had happened

The *diagnosis* is obvious The *prognosis* usually is considered to be poor, though Griffith and Mitchell state that a few cases may recover spontaneously *Treatment* should be by a psychiatrist

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Familial Tremor and Familial Nystagmus

Synonyms — Hereditary tremor hereditary nystagmus essential familial tremor essential familial nystagmus

Definition — An affection occurring in families consisting of a simple tremor of various parts of the body When the ocular muscles are involved nystagmus results

History — According to Critchley the first description of familial tremor in the literature is probably that by Most in 1836

Etiology and Occurrence — The etiology is unknown except for the fact that there is a strong familial tendency The condition may occur in several members of the same generation in successive generations or it may skip one or two generations It usually begins in early life sometimes even at or soon after birth sometimes in later childhood or adolescence The type showing nystagmus is especially likely to begin in the early days of infancy The age of onset may be more and more delayed in succeeding generations. Sometimes it does not appear until fairly late in life The hereditary transmission often shows interesting peculiarities for in some families only males may be affected in some only females in some there may be a crossed inheritance and in some both sexes may be affected indiscriminately Critchley quotes Minor to the effect that affected families tend to show marked longevity and fecundity, and also

that paralysis agitans has been known to affect a member of a family subject to hereditary tremor Roseno states that Cestan observed a case of hereditary tremor combined with muscular dystrophy

Pathology — This also is unknown Some writers have assumed that the extrapyramidal paths are involved but necropsies have failed to show recognizable changes Critchley believes there may be two types one due to dysfunction of the corpus striatum the other to cerebellar disturbance In support of the latter he cites the records of transitional forms between essential familial tremor and the rare cerebellar degenerations of later life

Symptoms — Many parts of the body may be affected including the head hands facial or ocular muscles lips tongue mandible larynx thoracic muscles lower extremities etc W R Brain states that the tremors may be generalized The tremors or nystagmus may develop gradually so that the patient is unaware of them in their incipiency but usually they are fully established within a year after their first appearance and remain constant throughout life The general health is unaffected When the larynx or respiratory muscles are involved there is a tremulous or breathless type of articulation Head tremors may be lateral (*tremblement negatif*) or vertical (*tremblement affirmatif*) The character of the tremor varies greatly in different individuals It may be fine and rapid like that of hyperthyroidism or coarse and slow like that of paralysis agitans It may be of static or intention type An effort of will may stop it for a second or two but no longer Otherwise it is constant during the waking hours but disappears during sleep Emotion fatigue and even talking may aggravate it. In old age a superadded senile tremor may make the condition worse

Diagnosis — The appearance of a constant tremor in childhood or youth disappearing in sleep without other abnormality and with familial incidence points to the condition When it develops later in life it can be mistaken easily for paralysis agitans *Paralysis agitans* however usually begins later in life with or without a history of epidemic encephalitis the muscular rigidity mask like facies and festinating gait of it are diagnostic With involvement of the hands both conditions affect the patient s writing but according to Critchley essential familial tremor does not show the micrographia of parkinsonism *Familial pseudosclerosis* shows a great variety of symptoms in addition to tremor including psychic changes apoplectiform attacks etc. *Simple senile tremor* may have a familial incidence at times but appears much later in life It is not certain that this latter is in any sense a different disease from the one discussed in this chapter In cases of *hereditary tremor* showing fine rapid oscillations of the fingers *hyperthyroidism* should be excluded *Neurasthenic tremors* lack the constancy of familial tremors and are easily recognized by the other symptoms of neurasthenia. *Multiple sclerosis* may be

confusing in its incipiency, but it is not a familial disease, and sooner or later shows many other defects involving speech, gait, changes in the reflexes, loss of sphincter control opthalmoscopic changes, etc

Prognosis — As stated already, the condition, once established, persists practically unchanged through life Any marked increase in the symptoms in old age probably is due to a superadded senile tremor

Treatment — There is no curative treatment Such drugs as stramonium, belladonna atropine and hyoscine may be tried in the hope of temporarily lessening the tremor slightly, but the philosophical patient may prefer to ignore his disability so far as practicable rather than to undergo prolonged treatment with so little benefit

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March 1 1937

PORENCEPHALY

Synonyms — Porencephalus porencephalia

Definition — A defect or defects in the brain substance communicating with the subarachnoid space extending deeply into the brain and usually communicating with the ventricular system The clinical picture depends on the site and extent of the lesion or lesions

History — According to Audry Reil published the first observation on porencephaly in 1812 considering it a rare case of absence of the corpus callosum in a thirty year old female idiot who died suddenly In 1859 Heschl first described the condition under its present name giving a detailed report of eight cases He believed that it was always associated with hydrocephalus In 1888 Audry collected 102 cases of varied etiology and in 1926 Schroer assembled from the literature 150 cases which he considered traumatic in origin

Etiology — For many years this was a controversial subject, but the consensus of opinion now is that the condition may result from inflammatory, vascular or traumatic factors, or a combination thereof Acute encephalitis is the chief inflammatory cause, and this often produces a secondary compression of the blood vessels in he areas involved, thus introducing vascular factors Syphilitic vascular lesions have been noted occasionally These various factors may

operate before or after birth and the traumatic factor often occurs during birth Pallasse and Guichard have described a post scarlatinal case

Pathology — This can be described simply as a cavity or cavities in the brain substance usually communicating with the ventricular system and opening into the subarachnoid space The extent of involvement varies greatly sometimes causing destruction of practically an entire hemisphere and even extending into the opposite side of the brain It may progress and enlarge much as does a syringomyelic cavity in the spinal cord *Indeed the two conditions rarely may be associated in one patient* Globus demonstrated histologic evidence of inflammation in his case the process beginning as a meningo-encephalitis in the parieto-occipital regions leading to strangulation of the blood vessels degeneration of the parenchyma proliferation of the glial elements and finally to scar formation in the cortex The condition progressed from the parieto-occipital regions to the temporal lobes then to the frontal lobes and finally to the midbrain and hindbrain Syphilis was absent

Levaditi Lepine and Schoen have studied the histopathology of the condition induced in rabbits by the production of experimental encephalitis They found the following sequence of events acute encephalitis later becoming chronic early inflammation and degeneration due to direct action of the virus on the brain tissue this in turn causing disorders of the blood and lymph *circulation by compression of the vessels A tendency to calcification was noted* in the tissue surrounding the cavity Hydrocephalus may or may not be associated with porencephaly and either macrocephaly or microcephaly may be present

Symptomatology — It is obvious from the pathology of the disease that the symptoms must vary greatly in kind and degree according to the location and extent of the lesions Thus idiocy imbecility hemiplegias sometimes of remarkably slight degree various other paralyses convulsions coma disturbances of sight and hearing headache and, indeed practically any phenomena referable to structural damage to any part of the brain may occur The most striking thing is the disproportionately tremendous amount of destruction of brain tissue that may occur with seemingly inadequate resulting symptoms Many examples have been reported in which it seems incredible that the patient could have lived to develop such extensive lesions Thus Wertkin reported the case of a boy living to the age of fifteen weeks in whom practically all of the left cerebral hemisphere and a part of the right frontal lobe were destroyed He seemed normal at birth but at the age of four weeks developed an irregular fever At ten weeks he showed a positive Kernig sign marked dermographia sluggish pupillary reaction to light and partial blindness His spinal fluid was normal Jelsma Spurling and Freeman describe a case in which there was destruction of most of the left occipital lobe in a left handed person without

confusing in its incipiency, but it is not a familial disease, and sooner or later shows many other defects involving speech, gait, changes in the reflexes, loss of sphincter control opthalmoscopic changes, etc

Prognosis —As stated already, the condition, once established, persists practically unchanged through life Any marked increase in the symptoms in old age probably is due to a superadded senile tremor

Treatment —There is no curative treatment Such drugs as stramonium belladonna atropine and hyoscine may be tried in the hope of temporarily lessening the tremor slightly but the philosophical patient may prefer to ignore his disability so far as practicable rather than to undergo prolonged treatment with so little benefit

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PORENCEPHALY

Synonyms —Porencephalus porencephalia

Definition —A defect or defects in the brain substance communicating with the subarachnoid space extending deeply into the brain and usually communicating with the ventricular system The clinical picture depends on the site and extent of the lesion or lesions

History —According to Audry Reil published the first observation on porencephaly in 181 considering it a rare case of absence of the corpus callosum in a thirty year old female idiot who died suddenly In 1859 Heschl first described the condition under its present name giving a detailed report of eight cases He believed that it was always associated with hydrocephalus In 1888 Audry collected 102 cases of varied etiology, and in 1926 Schroer assembled from the literature 150 cases which he considered traumatic in origin

Etiology —For many years this was a controversial subject, but the consensus of opinion now is that the condition may result from inflammatory vascular or traumatic factors, or a combination thereof Acute encephalitis is the chief inflammatory cause, and this often produces a secondary compression of the blood vessels in the areas involved thus introducing vascular factors Syphilitic vascular lesions have been noted occasionally These various factors may

treatment of ordinary epilepsy may also be tried when headache convulsions etc. are prominent symptoms Naturally if syphilis be present it should be treated

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Edgeworth's Disease

Synonym — Familial non renal subcutaneous edema of infants

History and General Discussion — In 1911 Edgeworth reported the cases of

demonstrable visual defect Such disproportion between pathology and symptomatology has led some to suggest that new centers or paths may be developed in sound parts of the brain to carry on the functions of the parts destroyed, as e g in corresponding parts of the opposite side of the brain

Bond reports the case of a 37 year old woman with a history of 'epilepsy', who had a right hemiplegia with atrophy of the muscles affected, who could not spit or whistle and who constantly drooled saliva She began to have fits at the age of 16 months, and the paralysis was noted then Her convulsive attacks were more or less periodic She also had pellagra, the symptoms of which recurred from time to time She became greatly emaciated before death The left hemisphere was atrophied with the cavity extending from the anterior to the posterior pole, there were no basal ganglia on that side An excess of cerebrospinal fluid was present

Berry and Bates record the case of an adult, female, retrograde imbecile, whose urine was loaded with albumin, and who had convulsions, flaccid paralysis of her right arm and leg incontinence of urine, outbursts of temper, dim vision diminished urinary output dying with typical symptoms of uremic coma, who was found at necropsy to have not only a severe nephritis but also porencephaly The cortex and convolutions of the brain were decreased in size, the fissures were imperfect parts of the hemispheres were absent, and the corpus callosum centrum ovale projection and association fibers and other areas of white matter were abnormally small

Diagnosis — It must be evident from the foregoing that diagnosis from the symptoms and physical signs usually is impossible In some cases, however, encephalography will reveal the defect This should be resorted to in cases with serious cerebral symptoms that cannot be explained satisfactorily by the clinical findings A negative encephalogram, however should not be taken as proof of the absence of the lesser degrees of porencephaly The condition usually is diagnosed as encephalitis, and, indeed this appears to be a frequent forerunner and cause of porencephaly but the clinical picture gives no key with which to determine the presence or absence of an abnormal cavity in the brain If a case should occur presenting major cerebral symptoms along with those of a concomitant syringomyelia the commoner cerebral diseases being excluded a tentative clinical diagnosis of porencephaly perhaps would be justifiable Usually the diagnosis is made at necropsy

Prognosis and Treatment — The outcome appears to be fatal in all cases The rapidity of the progress of the disease varies greatly, some patients dying a few weeks after the onset of symptoms, and others living more than a quarter of a century No effective treatment is known Jelsma Spurling and Freeman recommend surgical decompression in cases with severe persistent headache Fluid restriction, a ketogenic diet and other modern measures used in the

turcica in Thomas' patients point to a pituitary dysfunction. Prevention of the menstrual edema by hypodermic injections of a purified form of anterior pituitary-like sex hormone in one of Thomas' patients adds confirmatory evidence to this theory. Thomas suggests that the condition is the antithesis of diabetes insipidus. Sweeney points out that slighter degrees of edema *occur often in normal young women in association with menstruation (in 30 per cent* of 42 studied) and in a few it is enough to be noticeable as a pitting edema of the legs. Usually it is complained of as a tight or stuffy feeling in abdomen, hands or feet preceding or during menstruation and no actual pitting edema of the lower legs is noted. Okey and Stuart and Eufinger and Spiegler also have described similar findings accompanying menstruation. Atkinson and Ivy describe a patient with quite marked menstrual edema accompanied by frontal headaches, epistaxis and herpes simplex. Blood proteins were normal. Basal metabolic rate was −19 and thyroid brought the rate to normal but did not influence the edema. Pregnancy urine extract given to the patient lessened the edema while emmenin (Collip), an ether insoluble complex from placenta (12 cc daily) resulted in complete absence of the edema; theelol and theelin were ineffective. In the case reported by Molnar and Gruber there was no headache, basal metabolism was +18 and at another observation +25, and injections of an endocrine preparation, anteovin (combined ovarian and anterior pituitary substance) had no effect, while a mercurial diuretic (novurit) caused diuresis.

Symptomatology. — This is indicated in the previous section.

Diagnosis and Treatment. — Diagnosis of this type of edema is obvious if attention is given to the periodic repetition of edema in association with the menstrual cycle. It seems preventable or controllable at times by endocrine therapy with hormones of pituitary gonadal type as indicated in the section on pathological physiology. More exact knowledge of preparations to use, dosage, etc., in treating this form of edema awaits more detailed knowledge of the hormonal substances concerned in the menstrual cycle.

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six breast fed children in one family born to healthy parents, who developed subcutaneous edema at ages varying from one to fifteen weeks In one case it was slight and confined to the face, and the child recovered, in the other five death ensued in from one to sixteen weeks In three cases at least there was no albuminuria, and in two cases that came to necropsy no evidence of nephritis All the infants suffered from a marked diarrhea with green liquid stools, in some cases beginning only a few hours before the dropsy appeared Edgeworth pointed out that this was too rapid a development for what he called the ordinary dropsy of diarrhea in infants, or what we would call today a nutritional edema He believed that there was an inborn defect in the vessel walls so that even the slightest diarrhea caused dropsy, and that the condition was analagous to Milroy s disease and also to a hereditary tendency to erythema, urticaria etc He would also separate the condition from edema neonatorum on the grounds that that condition begins within a day or two of birth, usually in the lower extremities, that the edematous areas pit with difficulty, that the skin may be tense and shiny the temperature subnormal and the pulse slow and that the infant feeble and often premature, dies in from two to twelve days after birth Edgeworth discovered no effective treatment for the condition

The present writer has been unable to find any other reference in the literature to this disease

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Menstrual Edema

Definition —An extensive edema that occurs during the menstrual cycle

History —During recent years such a type of edema has been described by Thomas in 1933 Sweeney in 1934 Molnar and Gruber in 1934 and Atkinson and Ivy in 1936

Pathological Physiology —That the edema appears with the onset of menstruation suggests that its cause lies in a disturbance of those relationships which change from those of the intermenstrual period to produce the complete picture of the menstrual cycle Endocrine changes play an important part in this, both ovarian and pituitary So the edema reasonably may be considered as the result of some disturbance of balance in these endocrine functions An associated migraine choking of the optic discs and abnormality in the sella

The absence of vascular sclerosis inflammation or an obvious source of emboli are important diagnostic points Demonstration of the abnormal coagulability of the blood by Nygaard s technic establishes the diagnosis more firmly The test is somewhat complex and requires a skilled biochemist Those interested are referred to Nygaard s article

Prognosis and Treatment — The patient is liable to the formation of thrombi almost anywhere in the body with the dangers incident thereto No effective treatment has been devised for the condition per se When thromboses occur the treatment will depend on the location and extent of them Amputation may be required for gangrene of the extremities laparotomy for abdominal thromboses etc

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INTERMITTENT HYDRARTHROSIS

Synonym — Hydrops intermittens articulorum

Definition — Intermittent hydrarthrosis is a symptom complex rather than a specific disease characterized by more or less regularly recurring effusions into one or more joints with or without local inflammatory reaction or constitutional symptoms

History — Perrin reported the first case in 1845 according to Krida Moore recorded two more cases in 1864 and 1867 In recent years reports of the condition have been increasing in numbers

Etiology — This is varied and often poorly understood General factors such as age sex climate season social status etc have little or no predisposing influence Trauma may precede the onset of some cases and appear to be a factor but it plays no part in other cases Undulant fever appears to be the definite cause in some instances as Baker has demonstrated the *Brucella abortus* in the joint fluid but many cases are unassociated with that organism Gonorrheal and other forms of arthritis occasionally have shown the symptom complex as has syphilis Some cases are associated with certain allergic conditions such as asthma urticaria or angioneurotic edema One case has been attributed to gold therapy by Artagaveytia Formerly malaria was considered a cause but this view seems to have been largely abandoned in recent years

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March 1 1937

ESSENTIAL THROMBOPHILIA

Synonyms — Thrombosing disease, Nygaard Brown s disease

Definition — A condition characterized by episodes in which there is a pathologic increase in the coagulability of the blood plasma, causing a tendency to arterial and venous thromboses throughout the body, without inflammation or sclerosis of the affected vessels

History — This condition was reported in 1935 by Nygaard and Brown of the Mayo Clinic who noted that certain cases showing arterial thromboses differed from the generally recognized inflammatory or sclerotic vascular diseases They developed a test for determining plasma coagulability which established the condition as a definite entity

Etiology and Pathology — The essential feature is a fluctuation in the blood plasma coagulability a phenomenon which does not occur in those thrombotic diseases dependent on pathologic changes in the walls of the vessels involved The cause of this fluctuation is unknown

Symptomatology and Diagnosis — The symptoms are due entirely to vascular occlusion Usually this is sudden and involves a large vessel Arterial thrombosis appears to be more frequent than venous, but almost any vessels may be involved Repeated episodes of thrombosis may occur One patient was reported as showing thrombosis of the following vessels over a period of two years four digital arteries involving fingers of both hands, two involving a toe of each foot, a vessel in the left kidney (presumptive diagnosis based on hematuria) the central artery and vein of the right eye the right basilic and the left short saphenous veins Another patient in the same length of time showed occlusion of the right femoral artery a left renal vessel (presumptive as above), the left femoral short saphenous basilic and popliteal veins a superficial vein of the left thigh the right basilic vein and a superficial vein of the right lower quadrant of abdomen This was the only patient of the five reported by Nygaard and Brown who had more veins than arteries involved Two patients showed multiple arterial occlusion without venous involvement Gangrene frequently resulted from occlusion of arteries in the extremities Cerebral and cerebellar thromboses with the usual symptoms were noted Visceral thromboses were inferred from hematuria the signs of acute hemorrhagic pancreatitis etc Coronary thrombosis was not noted in any of the five cases

with aspiration of the affected joints followed immediately by the injection into the joint cavities of from 3 to 10 c c of a 5 per cent aqueous solution of quinine and urea hydrochloride Some of his patients apparently were cured in a few weeks by a single treatment some required as many as four treatments One case was reported as cured in which synovectomy had failed In one patient local pain after injection was so severe that the treatment had to be abandoned

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Hereditary Ectodermal Dysplasia of the Anhidrotic Type

Definition — An hereditary condition in which there is a lack of proper development of certain ectodermal structures notably the skin hair and teeth *Certain other parts of the body may be affected also in special individuals or groups*

History — According to Thannhauser Wedderburn in 1838 described ten cases in a Hindu family showing total absence of sweating deficient hair (scalp axillary and pubic) and partial absence or incomplete development of the teeth In 1848 Thurnam described two cases showing an associated ab

Pathology — Knda has studied this in synovectomy specimens and contrasts an active case with an inactive The active case showed a pale pink synovial membrane about a quarter of an inch thick with tab-like projections arranged in the form of somewhat flattened villi composed of recently formed granulation tissue showing many endothelial lined blood spaces and young fibroblasts, the tissue as a whole being markedly edematous The villi and immediately underlying tissue were notably infiltrated with lymphocytes There were also areas of dense connective tissue, fat and many sclerotic blood vessels

The inactive case showed long slender villi, well formed connective tissue only slight edema and very moderate round cell infiltration limited to the villi.

Symptomatology and Diagnosis — The recurrent effusions are diagnostic. The clock like regularity of the recurrences and remissions is extraordinary in some cases Baker s patient had a regular seven day cycle Some patients can actually predict the hour when an attack will appear Carter cites a story attributed to Garrod to the effect that Cambridge University arranged its athletic schedule so that certain matches would coincide with the remissions in the case of one of their athletes On the other hand, the cycle may be totally irregular or show more or less regular variations in periodicity Intervals of from a few minutes to several months have been described, an eight to eleven day interval being fairly common With multiple involvement the joints may be affected simultaneously or one may be at its maximum of swelling when another is at its minimum

A knee is affected most often with or without other joints. The onset is abrupt Pain in the joint increased by motion, may be of any degree of severity or quite absent it may precede the swelling by a few hours There may be merely a feeling of stiffness in the joint Redness of the surrounding parts is exceptional Fever may be absent or moderate as may leukocytosis. Slight headache anorexia and malaise may occur There may be a coincident urticaria with itching Menstruation may increase the symptoms decrease them or have no effect It is said that attacks tend to cease during pregnancy

Prognosis and Treatment — Recurrences may persist for years Spontaneous recovery may occur When some definite cause can be found and removed, cure may result but as a rule the condition is very obstinate

In the treatment obviously a cause should be sought If gonorrheal infection is present, fever therapy vaccines etc may be employed Syphilis should of course receive appropriate treatment Where specific allergens are demonstrated immunization may be attempted In cases showing *Brucella abortus* in the joint fluid or giving other evidence of undulant fever, brucella vaccine may be tried Radiation has been advocated Synovectomy apparently has proved effective as a last resort in some cases Ergotamine tartrate was advised by Weissmann Netter but recently he has reported some very striking results

had a normal rectal temperature equalled those of other children with a rectal temperature of 40 C (104 5° F) They recorded the skin temperatures as follows

	Patient (C)	*Standard* (C)
Face	35 2	33 2
Trunk	37 1	35 5
Extremities	37 8	33 0

The urine and blood have been reported normal and the Mantoux tuberculin test negative

Symptomatology — McKee and Andrews *sum up the clinical characteristics* as follows congenital absence of the sweat glands and piloscbaceous apparatus over most of the body marked dental aplasia depressed nasal bridge atrophic *rhinitis prominent supraorbital ridges thick protrusive lips thin glossy smooth* dry skin papular lesions on the face and heat intolerance The last symptom is especially distressing and makes hot weather well nigh unendurable to the patient Guilford s patient employed a boy in hot weather to pour water over his clothing as soon as it became dry

The general development and nutrition usually are good The hair on the scalp and in the axillary and pubic regions is sparse and lanugo like The eyebrows often are absent and the lashes very sparse Curiously enough the moustache and beard of some adult males have been well developed as in a case of Tendlau s Thannhauser however reports a lack of secondary sex hairs in his patient a 23 year old man The thin *smooth dry* parchment like skin is one of the most remarkable features of the disease It often feels abnormally warm to the touch In a number of cases various eruptions have been de*scribed such as milium xeroderma pigmentosa large superficial degenerated* sebaceous glands with hyperkeratosis dilated follicular orifices with surrounding acanthosis etc Thannhauser reports a pigmentation suggestive of Addison s *disease associated with low blood pressure*

The nails usually are normal but flat or even concave spoon shaped nails have been noted in a few cases Rarely the nipples and mammary glands have been defective or absent *No gross malformations of the nervous system* have been noted though a few patients have shown some mental deficiency Most of the reported cases however have shown a normal mentality Absence of *the lacrimal glands with resultant distressing xerophthalmia has been noted only in Thurnam s two patients Atrophic rhinitis with ozena is of frequent* occurrence and the ears may show dry impacted cerumen The lips usually are thick everted dry and wrinkled

The teeth display a striking picture when present at all Guilford s patient a man aged 48 was totally edentulous He was also unique in that he was *devoid of the sense of smell and almost so of taste Most cases show a few*

sence of the lacrimal glands apparently a unique observation in the literature of the subject In 1883 Guilford an American dentist, described a patient with the disease who was totally edentulous In addition he noted the existence of a saddle nose In 1886 Jonathan Hutchinson reported a case showing an associated absence of the nipples In 1929 Weech gave the condition the name by which it has since been known The disease is rare in its complete form though numerous cases of certain hereditary ectodermal defects have been reported Clouston alone having recorded 119 cases in six generations of one family with defective hair and teeth but not showing the absence of sweat glands

Etiology — Beyond the fact that the condition is an hereditary defect little is known Weech believes that this condition, as well as other ectodermal anomalies may arise as a result of a genetic mutation which occurs not by accident but as the occasional expression of a suppressed tendency to change inherent in the make up of the genes themselves An endocrine origin has been suggested and occasional cases have seemed to give some color to this view as for example Thannhauser s patient, whose symptoms suggested adrenal medulla insufficiency but nothing constant has been observed to point to any specific endocrine etiology The dry skin is due to a lack of development of the sweat glands and has no relation to myxedema Syphilis is not a factor as apparently no case has been reported so far that has shown any positive laboratory test for that disease The male sex predominates The condition is present at birth of course and becomes obvious in infancy, but as it does not appear to shorten life greatly it may be found in middle life or beyond Some observers have reported apparent transmission only by the female and inheritance only by the male while others have noted no sex linkage, but report transmission only by those affected with the disease Thannhauser would recognize two types of the disease on this basis Cole reports a defect of hair and teeth in cattle probably hereditary

Pathology — The gross structural changes will be noted under Symptomatology Histologically biopsies on the skin have shown complete or nearly complete absence of sweat and sebaceous glands and of hair follicles The basal metabolism usually has been found within normal limits, though Weech reported one case showing on three tests rates of +59 +37 and +29 per cent, respectively His other patient showed a rate of −10 per cent No remarkable changes have been noted in the blood chemistry except in Thannhauser s patient who had a low fasting blood sugar and a flat sugar tolerance curve Goeckermann states that the heat regulating mechanism is affected by the inability to sweat and Tendlau that the body temperature was not lowered by prolonged cold baths Hiebert and Garland using Talbot s technic noted that the skin temperatures on the face trunk and extremities of their patient who

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Acquired Anhidrosis with Circulatory Insufficiency

Synonym — Fog s syndrome

Definition — An acquired inability to sweat with circulatory insufficiency due to extreme vascular dilatation in the skin

History — Mogens Fog in 1936 reported such a case apparently unique in the literature

Etiology and Pathology — This condition developed in a previously well young man of normal appearance in sequence of severe prolonged paratyphoid fever The family history was free of sweat disturbances ectodermal dysplasia or metabolic abnormalities Histological study of the skin after the condition had lasted for six years showed about half of the sweat ducts of normal appearance and half abnormal cystic and lined with very flat cells This suggests that the disturbance chiefly was in the innervation of the sweat ducts and not solely a diseased condition of the skin itself

Symptoms — Having sweated normally before and during prolonged paratyphoid fever this young man thereafter never sweated Subsequently when he walked rapidly or engaged in manual labor especially out in the sunshine he soon felt indisposed his skin especially that of his face felt overheated he had dull precordial pain palpitation dyspnea and often painful paresthesias of the face and extremities These symptoms might last as long as an hour and leave him exhausted and unable to resume work Physical examination was negative except for a dry scaly skin There was no demonstrable neurological disturbance Numerous laboratory examinations were negative Urine output was increased averaging about 2000 c c per 24 hours

Artificial hyperthermia was tried to see its effect after nineteen minutes it was discontinued because he was exceedingly ill with dyspnea small weak and rapid pulse and rales at the bases of his lungs his skin was scarlet but devoid of sweat. Body temperature was normal with normal rhythmic fluctuations

Extensive tests indicated that there was nothing wrong with heat regulation

tusk like, scattered teeth, usually widely separated from one another X rays may or may not reveal additional unerupted teeth A "saddle nose" is very frequent and often leads to the suspicion of congenital syphilis Thannhauser however showed that in his cases, at least, the saddle nose was only apparent there being no true depression of the nasal bones but a projection forward of the frontal bones causing a relative depression of the bridge of the nose Hiebert and Garland report a case in a child who was always hoarse and who was subject to attacks of complete aphonia

Diagnosis Prognosis and Treatment — *Congenital syphilis* must be excluded by appropriate laboratory tests *Progeria* does not show so dry a skin or the dental defects and does show arteriosclerosis and usually renal disease, even in infancy

The condition obviously is permanent and incurable Patients with the disease should live in cool climates if possible Dental aid should be sought.

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Etiology and Pathology — This condition developed in a previously well young man of normal appearance in sequence of severe prolonged paratyphoid fever The family history was free of sweat disturbances ectodermal dysplasia or metabolic abnormalities Histological study of the skin after the condition had lasted for six years showed about half of the sweat ducts of normal appearance and half abnormal cystic and lined with very flat cells This suggests that the disturbance chiefly was in the innervation of the sweat ducts and not solely a diseased condition of the skin itself

Symptoms — Having sweated normally before and during prolonged paratyphoid fever this young man thereafter never sweated Subsequently when he walked rapidly or engaged in manual labor especially out in the sunshine he soon felt indisposed his skin especially that of his face felt overheated he had dull precordial pain palpitation dyspnea and often painful paresthesias of the face and extremities These symptoms might last as long as an hour and leave him exhausted and unable to resume work Physical examination was negative except for a dry scaly skin There was no demonstrable neurological disturbance Numerous laboratory examinations were negative Urine output was increased averaging about 2000 c c per 24 hours

Artificial hyperthermia was tried to see its effect after nineteen minutes it was discontinued because he was exceedingly ill with dyspnea small weak and rapid pulse and rales at the bases of his lungs his skin was scarlet but devoid of sweat Body temperature was normal with normal rhythmic fluctuations

Extensive tests indicated that there was nothing wrong with heat regulation

tusk like scattered teeth usually widely separated from one another X rays may or may not reveal additional unerupted teeth A saddle nose ' is very frequent and often leads to the suspicion of congenital syphilis Thannhauser, however, showed that in his cases at least, the 'saddle nose ' was only apparent there being no true depression of the nasal bones but a projection forward of the frontal bones causing a relative depression of the bridge of the nose Hiebert and Garland report a case in a child who was always hoarse and who was subject to attacks of complete aphonia

Diagnosis Prognosis and Treatment —*Congenital syphilis* must be excluded by appropriate laboratory tests *Progeria* does not show so dry a skin or the dental defects and does show arteriosclerosis and usually renal disease, even in infancy

The condition obviously is permanent and incurable Patients with the disease should live in cool climates if possible Dental aid should be sought

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March 1 1937

ACQUIRED ANHIDROSIS WITH CIRCULATORY INSUFFICIENCY

Synonym — Fog s syndrome

Definition — An acquired inability to sweat with circulatory insufficiency due to extreme vascular dilatation in the skin

History — Mogens Fog in 1936 reported such a case apparently unique in the literature

Etiology and Pathology — This condition developed in a previously well young man of normal appearance in sequence of severe prolonged paratyphoid fever The family history was free of sweat disturbances ectodermal dysplasia or metabolic abnormalities Histological study of the skin after the condition had lasted for six years showed about half of the sweat ducts of normal appearance and half abnormal cystic and lined with very flat cells This suggests that the disturbance chiefly was in the innervation of the sweat ducts and not solely a diseased condition of the skin itself

Symptoms — Having sweated normally before and during prolonged paratyphoid fever this young man thereafter never sweated Subsequently when he walked rapidly or engaged in manual labor especially out in the sunshine he soon felt indisposed his skin especially that of his face felt overheated he had dull precordial pain palpitation dyspnea and often painful paresthesias of the face and extremities These symptoms might last as long as an hour and leave him exhausted and unable to resume work Physical examination was negative except for a dry scaly skin There was no demonstrable neurological disturbance Numerous laboratory examinations were negative Urine output was increased averaging about 000 c c per 4 hours

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Extensive tests indicated that there was nothing wrong with heat regulation

under normal demand, lack of skin evaporation being compensated for by increased conduction and radiation If demand for the latter increased, compensation could be brought about only at the expense of marked, peripheral, vascular dilatation, enough to cause evidences of circulatory insufficiency as expressed by the symptoms already described

Treatment — Occupation with relatively little physical exertion was possible with no particular discomfort

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March 1 1937

Ichthyosis, Fever and Effort Syndrome

Synonym — Woodyatt s syndrome

Definition — A syndrome characterized by dry scaly skin, fatigue or exhaustion, dyspnea tachycardia, palpitation, tremors, dizziness, pains in the joints, fever and moderate leukocytosis the symptoms other than the ichthyosis appearing in warm weather increasing on effort, being relieved by rest and disappearing in cold weather

History — In 1935 Woodyatt reported this syndrome to the Association of American Physicians

Etiology and Pathogenesis — This is not completely understood However, in ichthyosis there are destructive changes with loss of function in the sweat glands and the contention of Woodyatt seems reasonable that this upsets the heat regulating mechanism of the body thus tending to produce the other disturbances characteristic of the syndrome It is doubtful though, if this explanation is fully adequate, for as Woodyatt points out ichthyosis is a common disease whereas his syndrome is a rare one Other conditions associated with decrease in the function of the sweat glands such as scleroderma hereditary ectodermal dysplasia of the anhidrotic type, myxedema etc, would also be expected to cause a like syndrome if the loss of the power to sweat freely were the sole cause Moreover it is a little difficult to explain the joint pains in Woodyatt s syndrome on this basis Woodyatt, therefore suspects some endocrine imbalance in addition to the interference with heat loss consequent upon the diminished function of the sweat glands He notes that Linser and Schmid have reported cases of ichthyosis with a temperature up to 102° F, rapid respiration and a basal metabolism as high as plus 40, but there were no

began About every two hours there would be a drenching sweat followed by a sharp drop in body temperature with a chill lasting from ten to thirty minutes followed by a gradual return of the temperature to its former level The cyclic fluctuations were less marked during sleep but occurred in lesser degree throughout the night The patient was exhausted and completely disabled He was moderately undernourished having lost about twelve pounds in weight His temperature fluctuated between 91° and 101° F His pulse rate was 100 per minute His blood pressure was 128/68 His eyegrounds were normal Nothing else of importance was noted in his history or physical examination to throw light on the condition

Roentgenograms of the head and thorax were negative The urine contained a small amount of albumin The hemoglobin was 15 9 gms per 100 c c erythrocytes 4 130 000 per cu mm leukocytes 4 800 per cu mm No malarial plasmodia were found Laboratory tests for syphilis typhoid fever the paratyphoids and undulant fever were negative At times the gastric acidity was normal but following a severe sweat the total acids showed a value of 14 and free hydrochloric acid was absent

A number of observations were made on the serum protein albumin globulin ratio plasma chlorides and hematocrit percentage of red blood cells at different stages during and following a cycle of clinical change

Possibly the changes noted are to be regarded as the effect of the sweats vomiting and therapy with sodium chloride rather than of any other significance

Diagnosis is obvious as the syndrome is unique

Prognosis — The patient was getting progressively worse until appropriate therapy was developed This seemed to offer an adequate means to control the condition but did not prevent their recurrence during a subsequent period of two and one half years

Treatment — Control of the sweating by atropine sulphate grain 1/50 (13 mgm) *every four hours did not influence the temperature curve* To replace sodium chloride loss calculated to be 12 grams per 24 hours enteric coated pills of sodium chloride 30 grains (2 gm) every four hours were given *Though the patient was stronger this failed too to control the fever Atropine* and sodium chloride were discontinued and the patient given sodium amytal 1½ grains (0 1 gm) every four hours for a sedative effect on the heat centers This controlled the fever very effectively One month later the patient reported a gain of 12 pounds in weight and that he was much stronger and free from sweats and chills with a normal temperature However later these periodic cycles have recurred but could be controlled fairly satisfactorily by the treatment with sodium amytal for the past six months he has had to take the sodium amytal more or less continuously

the latter showing a definite seasonal incidence, at least outside the tropics appearing in the warm months and disappearing in the cold, the relation of the symptoms to effort and their relief by rest, produce a clinical picture that can hardly be mistaken for anything else

Prognosis — So far as our present knowledge goes, only two factors have any beneficial effect, rest and a cool climate Without these the patient cannot expect any improvement

Treatment — Removal to a cool climate is essential to the patient's health. If this be temporarily impracticable, much of the patient s time will have to be spent in bed because of exhaustion and joint pains

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March 1, 1937

Intermittent Hypothermia with Disabling Hyperhidrosis

Synonym — The Hines Bannick syndrome

Definition — A syndrome characterized by intermittent attacks of nausea and vomiting followed by brief periodic cycles of sweating chills and a fluctuating temperature, which may reach extraordinarily low levels The latter symptoms constantly recur several times daily over a long period of time

History — The writer knows of but one case in the literature, that reported by Hines and Bannick at a staff meeting of the Mayo Clinic.

Etiology and Pathogenesis — All that can be said at present is that there is an extraordinary intermittent disturbance, probably of central nervous origin, affecting the vomiting vasomotor and heat regulating mechanisms thereby producing the characteristic symptoms and resulting in a depletion of the chloride content of the body Epidemic encephalitis has been suspected as the cause, but there is no proof of this thus far

Pathology — The reported case was not fatal so nothing is known about its pathology Clinical pathology will be discussed under the next heading

Clinical Picture — The patient of Hines and Bannick was a 22 year old man who for ten years had had annual attacks beginning in December or January and lasting from four to six weeks In 1934, however, the attack, though beginning in January as usual, persisted until August when the patient was admitted to the Mayo Clinic

The onset of every attack consisted of a five to seven day period of nausea and vomiting following which the extraordinary cycle of chills and sweats

Some authorities consider the condition as analogous to von Recklinghausen's disease except that the latter involves chiefly the fibrous tissue whereas the Ehlers-Danlos syndrome involves especially the elastic tissue Neuromata of the cutaneous nerve endings have been described in connection with the syndrome Slight trauma that would have no appreciable effect on normal skin or at most cause slight bruising often will split the skin open in a patient with the Ehlers-Danlos syndrome as noted in the definition and as also noted this fragility is especially evident on the exposed portions of the body and over the bony prominences These split areas may become infected and suppurate before healing hence extensive scarring of the skin is frequent The scars may be bluish brownish or white in color Often the typical pseudotumors develop at the site of trauma. They are composed chiefly of blood and vascular tissue often resembling angiomata with complicating small hematomata Usually they are violaceous or bluish in color and bear some resemblance to raisins Prolonged pressure from firmly applied dressings will cause them to decrease in size and finally disappear usually within two or three weeks Epidermolysis bullosa has been noted in some cases rather than the usual hemorrhagic pseudotumors

The Joints —The extreme laxity of these may be very striking especially in the metacarpophalangeal joints Dorsal flexion hyperextension of the fingers and thumbs may be possible to almost as great a degree as palmar flexion the patient being able to touch the dorsum of the hand with the tips of the digits of that hand The elbows and knees may also be affected to a marked degree Permanent dislocations have been described In other cases simple traction may dislocate a joint with great ease the distal bone snapping back into place immediately on its release

Hyperelasticity of the skin with or without the fragility and tendency to pseudotumor formation may exist without abnormal laxity of the joints and lax joints may occur without dermatologic disturbances but such manifestations do not constitute the true Ehlers-Danlos syndrome The India rubber skin men and women of the side shows have hyperelastic skin of the type we have been considering The Germans call the condition *Gummihaut*

The Ehlers-Danlos syndrome becomes obvious early in life usually within the first decade A number of associated congenital conditions have been described in individual cases Tobias lists the following lymphangiectatic tumors syringomyelia von Recklinghausen's disease fibromata fibrous tumors with nevi acrocyanosis clubfoot supernumerary teeth and mental deficiency Tobias's own patient with a complicating congenital lipomatosis has been mentioned already

Diagnosis Prognosis and Treatment —The diagnosis is obvious The fundamental underlying condition is not amenable to treatment and is permanent

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March 1 1937

EHLERS-DANLOS SYNDROME

Synonym — Danlos syndrome

Definition — A syndrome exhibiting four major characteristics, viz 1 excessive elasticity of the skin, 2 abnormal fragility of the skin, especially that covering bony prominences and exposed parts so that it tends to split open as a result of very slight trauma, 3 a tendency to develop peculiar molluscoid pseudotumors of the skin in response to trauma, 4 abnormal laxity of the joints

History — Ehlers seems to have given the first clinical report of the syndrome in 1901 In 1906 Hallopeau and de Lepinay described another case, but diagnosed it incorrectly as juvenile pseudodiabetic xanthoma Two years later Danlos studied the same patient found that the supposed xanthomata decreased in size with compression and emphasized the importance of the elasticity of the skin Pautrier found on biopsy that the swellings were not xanthomata but masses of loose cellular tissue containing dilated blood vessels that had developed as the result of trauma In 1932 Schulmann and Levy Coblentz reported a case in a 25 year old woman who showed generalized cutis laxa articular laxity especially of the metacarpophalangeal joints and violaceous flabby soft raisin like tumors on the elbows and fingers and called the condition Danlos syndrome after the man who had given the most adequate description of it In 1934 Tobias recorded the first case in American medical literature It was complicated by congenital lipomatosis In the same year Poumeau Delille and Soulie reported a case under the name of the Ehlers-Danlos syndrome

Etiology — This is entirely unknown Some familial cases have been reported others have shown no such incidence

Pathology and Symptomatology — These are so intimately associated that they can be discussed best together

The Skin — This is hyperelastic and can be pulled away from the underlying tissues to an abnormal degree When so pulled and then released, it retracts completely This differentiates it from the dermatolysis found in von Recklinghausen s disease multiple neurofibromatosis Histologically there is great excess of elastic tissue from three to four times the normal amount.

the *Haverhillia multiformis* Usually it occurs in milk borne epidemics though sporadic cases have been reported

History and Epidemiology — In May and June 1925, an epidemic occurred in Chester Pa which was thought at first to be dengue It was studied by the Pennsylvania Board of Health About 400 cases were discovered and it was estimated that about 600 probably occurred No *Aedes ægypti* mosquitoes could be found in the infected area and the outbreak was soon traced to a milk supply Ninety two per cent of the patients used raw milk from a certain bottling plant Some of the workers in the plant and some living on farms supplying the plant with milk were also affected About 20 per cent of the persons using the milk developed the disease whereas only about 0 5 per cent of the general population did so Nothing further of importance regarding the nature of the disease was learned at this time

In January 1920 an epidemic of about 60 cases broke out in Haverhill Massachusetts It was limited to a strip of territory running for about a half a mile along a river and served by a dairy selling raw milk in violation of the Massachusetts state health laws The season precluded any mosquito-borne disease The first cases became ill January 12th the last case January 9th On January 22nd Dr Carl Mindlin saw eight cases and brought the matter to the attention of the health authorities Dr Edwin H Place with a group of workers from the Boston City Hospital was asked to study the outbreak Their investigations established the disease as a definite entity clinically and bacteriologically and they called it erythema arthriticum epidemicum More recently it has come to be known as Haverhill fever The largest number of cases in one family was eight The use of pasteurized milk promptly stopped the epidemic

A few sporadic cases have been reported following the bite of a rat and it is probable that similar cases have been erroneously diagnosed as rat bite fever

In 1926 Levaditi Nicolau and Poincloux reported an infection occurring in one of them personally from which they isolated an organism that they called *streptobacillus moniliformis* which probably is identical with that found in the Haverhill epidemic

Etiology and Pathology — As stated above there was abundant evidence to show that the epidemics were milk borne though the milk showed negative bacteriological findings However ten out of twelve blood cultures made from Haverhill patients yielded a special microorganism studied by Parker and Hudson and named by them Haverhillia multiformis It was also isolated in two cultures from aspirated joint fluid It is Gram negative and as its name suggests takes varied forms running from a coccobacillus through straight and curved rods to long filamentous looped or branching forms often showing oval or spherical enlargements It grows well on blood agar but poorly on milk

Except for a greater exposure to the risk of septic infection than normal because of the unusual susceptibility of the skin to injury, there is no evidence that life expectancy is affected Care should be taken to avoid even minor trauma to the skin and when such injury does occur, suitable measures should be taken to avoid infection of the wounds Dry dressings should be applied over the pseudotumors in such a way as to produce firm compression of them When the laxity of the joints seriously handicaps function, or when permanent dislocations occur orthopedic measures, operative or non operative, may be required

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March 1 1937

HAVERHILL FEVER

Synonym — Erythema arthriticum epidemicum

Definition — An acute exanthematous fever associated with pain and usually with swelling in certain of the larger joints, due to a specific organism,

to escape and only one case has been noted of involvement of the sternoclavicular joint The vertebral articulations may be affected in some patients as they may show great pain on turning over or moving the back The joints may show nothing objectively but usually they are swollen and red often to a marked degree and there may be obvious fluid in the capsule The pain and disability may be very severe especially in the latter part of the acute illness and may last from three or four days to several weeks It is not uncommon for all but one joint to clear up in a few days but for that to give trouble for some weeks In two cases aspiration of a joint has yielded a yellow cloudy fluid showing a slight flocculent precipitate on standing containing polymorphonuclear leukocytes

A few patients have shown some cough and sore throat with a diffuse redness of the throat extending over the soft palate Two cases were reported as developing a mild bronchopneumonia on the third and fifth day of the disease respectively lasting about a week

Delirium is unusual but has been described as varying from attempts to get out the window to a semistupor The heart does not appear to be affected Nothing remarkable has been reported in the urine Blurred vision photophobia burning and tingling of the hands and feet and stabbing needle like pains in the forearms are among the rarer symptoms reported

Blood — A mild hypochromic anemia has been found The white cell count has run from 6 800 to 19 000 per cu mm with an average of about 12 000 The differential count is normal Dark field studies of the blood have been negative

Diagnosis — This should not be difficult in an acute epidemic limited to the users of a raw milk supply who show an acute febrile onset with chills vomiting headache etc followed by a blotchy eruption involving the extremities particularly and showing a tendency to develop petechiae these phenomena in turn followed by or associated with a multiple arthritis The arthritis distinguishes it from most of the other exanthemata A few conditions require more detailed differentiation

Rheumatic fever could hardly be confused with the epidemic form The eruption blood cultures and freedom from carditis should differentiate the sporadic form In contrast to *dengue* Haverhill fever may occur in winter when there are no mosquitoes it more often shows definite swelling of the joints pains in the eyeballs and suffusion of the face so common in dengue are absent and the joint symptoms tend to last longer than in dengue The results of blood culture should be decisive

Undulant fever has much in common with Haverhill fever Both are milk borne and show fever eruption and painful joints In Haverhill fever however the pain does not shift about from joint to joint there is no splenic enlarge

which may explain why it could not be isolated from the milk of the infected herd The herd had been pronounced healthy by state veterinarians, but one reactor cow was found, whose serum strongly agglutinated the organism She had a superficial lesion on one teat and another teat that dripped milk constantly Later on attempting to purchase her for pathologic study, it was learned that she had been sold to a butcher and the carcass was not obtainable In the epidemics that have been studied no case of contact infection has been recorded Raw milk appears to have been the sole means of transmission in the epidemic cases

Rat bite seems to be the most frequent cause of the rare sporadic cases Scharles and Seastone discuss in detail this phase of the etiology, and the reader is referred to their able article for further data

To date the mortality of the disease has been nil so nothing is known of the pathological changes in man other than what is revealed by the symptomatology and clinical laboratory studies

Symptomatology — The incubation period in the few cases in which it has been determined was brief about three days This was true in the case of a man who came to Haverhill to nurse his father He contracted the disease three days after his arrival during which time he used the infected milk A similar brief period has been the rule in the sporadic cases following rat bite

The onset usually is sudden often showing severe chills, vomiting, intense headache malaise and prostration The vomiting and chills may be only initial or may persist for as long as three days Dizziness may occur The temperature at onset usually reaches 103° to 105° F but drops to normal or nearly so on the third or fourth day with subsequent rises and remissions, rarely reaching the initial height this prolongs the febrile period to two weeks or more

On the first to the third day a dull red blotchy irregular discrete maculopapular eruption appears usually on the extremities and especially on their extensor aspects and about the joints In severe cases the shoulder girdle trunk and face may be involved The lesions vary greatly in shape and arrangement, being from one to four millimeters in diameter sometimes morbilliform, at others suggesting the eruption of rubella The rash usually increases for from one to three days lasts about a week and then fades leaving moderate pigmentation for about two weeks In a mild case the exanthem may last but a day Petechiæ may occur on the feet including the toes and soles for several days after the eruption has faded from the upper extremities The tourniquet test shows marked hemorrhage into the lesions A fine desquamation occurs in about twenty per cent of the cases

The joints become involved from the first to the eighth day usually about the third Multiple involvement is the rule varying from two to practically all the large joints and often affecting the fingers and toes as well The jaws seem

to escape and only one case has been noted of involvement of the sternoclavicular joint The vertebral articulations may be affected in some patients as they may show great pain on turning over or moving the back The joints may show nothing objectively but usually they are swollen and red often to a marked degree and there may be obvious fluid in the capsule The pain and disability may be very severe especially in the latter part of the acute illness and may last from three or four days to several weeks It is not uncommon for all but one joint to clear up in a few days but for that to give trouble for some weeks In two cases aspiration of a joint has yielded a yellow cloudy fluid showing a slight flocculent precipitate on standing containing polymorphonu clear leukocytes

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Undulant fever has much in common with Haverhill fever Both are milk borne and show fever eruption and painful joints In Haverhill fever however, the pain does not shift about from joint to joint there is no splenic enlarge

ment and neuritis orchitis and lymphocytosis do not occur The course of undulant fever is much longer and it never shows an explosive outbreak affecting a large proportion of persons using a given milk supply such as occurs in Haverhill fever Blood cultures agglutination tests, etc, decide in doubtful cases

Erythema multiforme shows larger lesions and negative blood cultures *Anaphylactoid purpura* usually shows less fever at onset, chills are unusual, and severe abdominal pain hematuria and melena are likely to occur The eruption is purpuric throughout and the course much more prolonged as a rule than is that of Haverhill fever It never occurs in explosive epidemics

Rat bite fever of spirillum etiology usually shows a longer incubation period The *spirillum minus* may be demonstrated by puncture and aspiration of lymph nodes in the vicinity of the bite, or sometimes by dark field examination of the blood If these methods fail inoculation of a mouse with the patient s blood taken during a febrile period should show the spirillum in the mouse s blood eight or ten days later Rat bite fever yields promptly to neoarsphenamine, whereas Haverhill fever is little affected by it Another type of fever following rat bite and due to a streptothrix might be a little more difficult to distinguish Possibly this may be the same disease as Haverhill fever although there seems to be a difference in clinical picture For a discussion of rat bite fever see Vol V Chapt XXX-B

Prognosis and Treatment — The prognosis appears to be uniformly good, though a patient with severe joint symptoms may take several weeks to recover

Treatment is symptomatic Analgesics are indicated for the joint pains Salicylates give little or no relief Where there is marked effusion into a joint aspiration may be beneficial Splinting may help in some cases

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March 1 1937

Dystonia Musculorum Deformans

Synonyms —Dysbasia lordotica progressiva torsion spasm tortipelvis dystonia lenticularis Ziehen Oppenheim disease

Definition —A syndrome based on organic disease of the brain in which there are profound disturbances of muscle tonus coupled with a loss of the power of inhibition of voluntary muscular activity resulting in gross uncontrollable incoordinated bodily movements of varied and strikingly bizarre nature The disease usually is progressive but may become stationary for a considerable period at any stage of its development

History —In 1910 under the name of progressive torsion spasm Ziehen mentioned five cases of this condition at a meeting of the Psychiatrischer Verein in Berlin Accounts of three of these cases had been published already in 1908 by W Schwalbe according to Diller and Wright but he had considered them as allied to impulsive tics The condition was very generally confused with Huntington s chorea hysteria and various motor tics until Oppenheim s publication in 1911 established it as a clinical entity

Etiology —Like that of the Parkinsonian syndrome this probably is varied Some cases appear to be due to epidemic encephalitis Foxe recognizes two etiologic groups encephalitic and idiopathic A very few familial cases have been mentioned Age seems to be a strong predisposing factor as the vast majority of cases begin in childhood and practically all before middle age

Pathology —This also seems to be somewhat varied Conat believes that the lesions probably are in the putamen or caudate nucleus Hunt also localizes the trouble in the corpus striatum whereas Jelliffe placed it somewhere along the cerebello-thalamo-cortical arc E W Taylor also thought that the cerebellum should be considered as a possible site of the trouble He Wechsler

ment and neuritis orchitis and lymphocytosis do not occur The course of undulant fever is much longer and it never shows an explosive outbreak affecting a large proportion of persons using a given milk supply such as occurs in Haverhill fever Blood cultures agglutination tests, etc, decide in doubtful cases

Erythema multiforme shows larger lesions and negative blood cultures *Anaphylactoid purpura* usually shows less fever at onset, chills are unusual and severe abdominal pain hematuria and melena are likely to occur The eruption is purpuric throughout and the course much more prolonged as a rule than is that of Haverhill fever It never occurs in explosive epidemics

Rat bite fever of spirillum etiology usually shows a longer incubation period. The *spirillum minus* may be demonstrated by puncture and aspiration of lymph nodes in the vicinity of the bite, or sometimes by dark field examination of the blood If these methods fail inoculation of a mouse with the patient's blood taken during a febrile period should show the spirillum in the mouse's blood eight or ten days later Rat bite fever yields promptly to neoarsphenamine, whereas Haverhill fever is little affected by it Another type of fever following rat bite and due to a streptothrix might be a little more difficult to distinguish Possibly this may be the same disease as Haverhill fever, although there seems to be a difference in clinical picture For a discussion of rat bite fever see Vol V Chapt XXX-B

Prognosis and Treatment — The prognosis appears to be uniformly good though a patient with severe joint symptoms may take several weeks to recover

Treatment is symptomatic Analgesics are indicated for the joint pains Salicylates give little or no relief Where there is marked effusion into a joint aspiration may be beneficial Splinting may help in some cases

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ter disturbance is absent Sensory changes are rare other than muscle pains due to excessive effort Disturbance of speech may occur but is unusual The knee jerks may be increased diminished or normal Facial grimacing has been noted in a few cases Occasionally the symptoms may suggest cerebellar disorder Hypertrophy of the cramping muscles may occur Mental excitement attracting the patient s attention to his condition and especially the erect position and walking bring out the movements in their most characteristic form In some cases while the muscles involved in the abnormal movements are hypertonic other muscles, especially those of the neck may be hypotonic so that the head may fall forward on the chest This is not essential to the picture however Diller and Wright mention a myotonic reaction in some of the muscles of the forearm Voluntary movements are performed as if there were a conflict between agonistic and antagonistic muscles Monoplegic hemiplegic and diplegic forms have been described Even at rest in severe cases bizarre movements may continue, though they disappear during sleep Such a bewildering variety of abnormal movements occurs in different cases that it is impossible to describe them all Among others the following have been noted a tendency to hyperextend one or both legs at the knee and to rotate the leg outward in walking hyperextension of the back in a sitting posture with jerky movements of the buttocks, a jerking backwards of the body with every step when walking waddling like a duck with the knees and hips semiflexed jerky movements of the arms on attempting to grasp something etc The writer saw a patient who exhibited the most violent jerking and swaying movements on walking who also on attempting to pick up a pencil or some other small object, developed violent jerky contractions of the fingers which would project the object almost across the room The attitudes and movements have been described as clownish Keschner has given the most detailed analysis of the abnormal movements and postures in any case report in the literature known to the present writer Of special interest was the fact that the first symptom the patient noted was that she could walk backwards as easily as she could forwards Though she developed extreme contractures along with extraordinary movements in her legs during sleep they straightened out and became quiet It was also remarkable how she could thread a needle despite her clumsiness and spasms

Weisenburg has reported a case in which the phenomena were confined largely to the muscles of the upper chest shoulders neck and jaw Wechsler and Brock noted decerebrate rigidity in some cases They recognize two types of dystonia myokinetic and myostatic i e cases with and without involuntary movements when the patients are at rest Urechia and Mme Retezeanu report a case with dysphagia and dysarthria and with an open drooling mouth

and Spiller have commented on the coexistence of cirrhosis of the liver in some cases, thus suggesting an etio-pathological relationship with Wilson's progressive lenticular degeneration Keschner states that the calcium metabolism was found normal in one case in which it was studied Winner described cellular degeneration and neuroglial changes in the caudate and lenticular nuclei, in the dentate nucleus of the cerebellum, in the thalamus, pons and cerebral cortex, resembling those of pseudosclerosis Those in the corpus striatum were not more marked than elsewhere Wechsler feels that Wilson's lenticular degeneration pseudosclerosis and dystonia musculorum deformans may be variations in clinical expression of a single pathologic process Davison and Goodhart found degenerative lesions in the post central, superior parietal and insular convolutions and in the neostriatum The muscles rarely show any changes other than the fact that in some cases there is hypertrophy of those muscles subject to great and constant strain Diller and Wright mention "an inexplicable non degenerative atrophy" in some of the small muscles of the hand in a few cases

Symptomatology — As already noted, this is striking and bizarre in the extreme Usually the muscles of locomotion are involved most The onset ordinarily is in childhood occasionally in young adult life, and the clinical picture develops more or less gradually At first peculiar jerky movements may appear in any or all of the extremities combined with muscular stiffness or even contractures A spastic scissors gait may develop, there may be a waddling gait much like that of progressive muscular dystrophy, or the gait may suggest hysteria very strongly The muscular disturbances tend to diminish *or cease when the patient is at rest, but they reappear* at once on any attempt at voluntary movement. The posture may be very bizarre and the gait of a swaying "dromedary" type The condition may be monosymptomatic at onset i e one hand or one foot may show the peculiar spasms, and the trouble may not spread for years Usually however, it becomes widely spread throughout the body rather quickly As Diller and Wright state, the abnormal movements are hard to describe being neither tremors tics nor athetoid movements though suggestive of all They are uncontrollable spasmodic movements of any or all the extremities the head, trunk, etc, and they seem like convulsive movements which the patient is trying desperately to control When they involve the whole body, they might well be described as the movements of a person trying to wrestle with himself With extensive involvement of the muscles of locomotion there is very rapid fatigue on walking so that covering a distance of a few feet may exhaust the patient completely, causing him to exhibit a flushed face, profuse sweating and evidences of severe strain from the exertion required There is no true paralysis usually there is no atrophy there are no electrical changes in the muscles, and sphinc

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Tick Paralysis

Definition —A disease of certain animals and of man consequent upon the bites of various ticks of the genera *Dermacentor, Hæmaphysalis* and *Ixodes* characterized by a group of acute neurologic symptoms the most striking of which are muscular incoordination staggering and flaccid paralysis If the ticks are removed on the appearance of symptoms recovery usually is rapid if not death may result

History —According to Whitmore Bancroft in 1884 noted that in Australia dogs and cats often die from muscular paralysis following tick bite and he also reported a case of tick bite in a woman followed by weakness and blindness For many years sheep farmers in Australia South Africa and in certain regions of the Rocky Mountains notably in British Columbia Montana Idaho Washington and Oregon have been familiar with a paralytic disease affecting their sheep which they have attributed to tick bites *In 1905 Borthwick reported his study of such* an outbreak in sheep and lambs In 1912 Temple in Oregon and Cleland in Australia reported paralysis in children associated with tick bite and Todd collected reports of a number of cases from physicians in British Columbia In 1913 Hadwen studied tick paralysis in sheep and in man and Hadwen and Nuttall produced experimental tick paralysis in dogs In 1933 Wallace Cahn and Thomas reported studies of moose disease

Diagnosis — In its early stages dystonia musculorum deformans readily may be confused with *hysteria*, and perhaps certain *motor tics* The wild in coordinated movements of *Huntington s chorea* may be easily confused with the fully developed case of dystonia, but in the former the mentality is impaired with irritability, explosive outbursts of temper and a progressive dementia whereas the intelligence in dystonia is normal, a familial incidence is the rule in Huntington's chorea and the exception in dystonia, the age of onset usually is much later in Huntington s chorea Goodhart states that one of his cases of dystonia was differentiated from Huntington s chorea only by careful analysis aided by slow moving pictures

Prognosis — The condition usually is slowly or rapidly progressive, though according to Hunt it may become stationary

Treatment — Orthopedic treatment, such as the application of plaster casts section of tendons, etc has failed to give relief Intraspinal injection of magnesium sulphate causes temporary paralysis of muscles but confers no lasting benefit Putnam gives us a therapeutic ray of hope He reports improvement from operative section of the prepyramidal and anterior quadrant marginal fibers or the latter alone in the cervical cord In one case the operation was followed by mild signs of pyramidal tract defect and in another by hemianalgesia but no permanent ill effects have been noted The treatment is probably too new for final evaluation but is certainly worthy of trial

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lower extremities first then the upper, and, if the tick is not found and removed the more vital muscles concerned with swallowing and respiration If death occurs it is almost always due to paralysis of the muscles of respiration though death in a convulsion has been reported A classic description of the symptoms has been given by Bassoe in reporting a case in a forty year old university professor who was spending a vacation in Colorado One afternoon he started on a walk feeling well On his way home his gait became unsteady That evening his fingers felt numb and prickling but there was no pain He had to get up in the night and staggered badly He slept well The next morning he could walk only by holding on to a chair His palms were numb and his toes tingled his vision was blurred, he had slight diplopia and he noted some nausea when his eyes were open On the morning of the third day there were partial retention of urine and incontinence of feces His face tongue and left ear felt numb, and his whole face seemed stiff He had difficulty in swallowing His temperature was subnormal and his hands and feet felt cold He noted some dyspnea He could pull his feet up but did not feel his toes move He had no numbness above his wrists After two hours sleep that afternoon his visual disturbance was less marked He could not touch his finger to his nose without banging his face At 6 P M a greatly engorged wood tick was found embedded in his left groin An incision had to be made to remove the tick intact There was an ecchymotic area the size of a silver dollar around the bite but no abnormal sensation was noted here before or after removing the tick The patient s knee jerks were absent at this time The next day he felt much better had no dysphagia or dyspnea and had much less difficulty with his bladder He still staggered and his hands felt numb but there were no abnormal sensations in his feet The day after this he could walk without support He felt no numbness until he had sat up for an hour when the fingers of his left hand again felt numb The following day the sixth day of his disease and the third day after the removal of the tick all the subjective symptoms had gone A week later his tendon reflexes were normal and he seemed well except for the fact that he tired easily on climbing a hill contrary to his usual facility in this exercise This tendency to fatigue soon disappeared The tick was identified as *Dermacentor venustus*

Other symptoms that have been noted by various observers include dilated pupils with loss of the light reflex inability to execute movements rapidly (the first symptom noted in one case) exaggeration of tendon reflexes preceding their loss emotional excitability twitching choreiform movements apathy incontinence of urine the feeling of a lump in the throat dysarthria swollen tongue tachycardia etc Urinalysis in one case gave negative results The writer has not found a record of other laboratory studies

Diagnosis — This should not be difficult in most cases in localities where

in Ontario isolated a specific microorganism *Klebsiella paralytica* from the intestinal contents of ticks found on the affected moose reproduced the disease by injecting the organisms into a healthy moose and pointed out the similarity if not the identity of that disease with the tick paralysis of sheep and man In 1938 Robinson and Carroll reported tick paralysis of man in Georgia and in 1940 Townsend and Nash reported its occurrence in the Carolinas

Etiology and Pathogenesis — It is fully established that the disease is dependent on the bite of a tick The exact method of production of the disease is unknown There is much to suggest that some toxin is responsible for the symptoms especially the extraordinarily rapid recovery of most patients on removal of the ticks Some have suggested that the definite incubation period of the disease would seem to predicate an infectious rather than a toxic cause and suggest that the tick is merely a vector

Distribution — Tick paralysis has been noted in various parts of Europe in South Africa Somaliland, Australia British Columbia Washington Oregon Idaho Montana Wyoming Colorado Georgia and the Carolinas If the moose disease of Ontario is identical with tick paralysis then that province must be included also McCornack believes that very many unreported cases occur in Idaho Montana Washington and Oregon Sheep are affected much more frequently than other domestic animals The disease has been reported also in the dog cat colt rabbit and grouse

Clinical Course — The writer has found no record of a necropsy in man so nothing can be said regarding the pathological anatomy of the disease Children are affected much more frequently than adults It has been suggested that this may be due in part to the fact that adults are more likely to notice ticks on their bodies and remove them promptly There is a definite incubation period of six to seven days Fever is absent or slight at onset as a rule and the temperature characteristically becomes subnormal about the second day of the disease Faust however describes considerable fever at onset the temperature reaching 104° F Marked irritation ecchymosis ulceration or infection with swelling of the regional lymph nodes may occur at the site of the bite but these local phenomena are not an essential part of the disease occurring often with any ordinary non paralyzing tick bite In some of the cases observed before the condition became a familiar one the paralytic phenomena seemed to appear out of a clear sky and the offending tick was not discovered or suspected until late in the disease or even until after death Often the first symptom noted is a tendency to fall when running Along with this or shortly after its appearance an unsteadiness of gait develops Usually within a day or two a flaccid paralysis of ascending type appears involving the

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March 1 1941

Acrocephaly

Synonyms — Acrocephalia acrocephalus beaten silver skull caput turritum hypsicephalia hypsicephalus hypsicephaly oxycephalia oxycephalus oxycephaly Spitzkopf steeple head tete à la Thersite tete a tour Thurmschadel tower head

Definition — Acrocephaly is a condition in which the cranium is abnormally high and more or less pointed Authorities differ slightly as to just what constitutes abnormal height of the skull some considering a vertical index above 75 1 as abnormal others an index above 80 (The vertical index is the number obtained by multiplying the height of the skull by 100 and dividing by the length) The term acrocephaly is derived from the Greek ακρος point and κεφαλη head The prefix in hypsicephaly comes from the Greek ὕψι high and that in oxycephaly from οξυς meaning sharp Extreme cases are interesting as anomalies but the chief clinical interest lies in certain disturbances which very frequently are associated with the condition notably visual defects which may vary from high grade myopia to total blindness exophthalmos some

sheep or other domestic animals are frequently affected In every case of acute flaccid paralysis in tick infested regions, a careful search should be made for ticks on the patient's body They are easily missed in hairy regions, if the search is not thorough Some authorities believe that paralysis is more likely to follow tick bites close to the spine or in the occipital region than elsewhere, and that it is more severe under such conditions, but the whole body should be inspected meticulously for ticks

Prognosis — If the offending ticks are found and removed promptly during the early symptoms, the prognosis should be good When extensive paralysis has occurred, especially of the respiratory muscles it is more serious If death does not result recovery will be complete McCornack states that it is not positively known whether recovery can occur without removal of the tick In thirty seven cases, including five adults reported by various authors there were eight deaths, all in children giving a mortality of 21 6 per cent. This series, however includes some of the early cases in which the role of the tick was unsuspected With prompt removal of the ticks before extensive paralysis develops, the mortality should be greatly reduced In most cases recovery is a matter of only a few days

Prophylaxis — In livestock proper dipping in parasiticides is indicated In man suitable clothing with close fitting neck and wrist bands and boots should be worn in tick infested areas Most important of all ticks should be searched for every time the clothing is removed and if found removed Clearing and dragging land has reduced the number of ticks in certain areas Experiments are being made by the United States Public Health Service in the introduction of parasites which prey on ticks As in animals one attack confers immunity to the disease

Treatment — Ordinarily the only treatment required is to look for, find and remove all ticks on the body of the patient If the tick is firmly attached a little chloroform or kerosene should be put on it to make it relax its hold Care should be taken to remove the tick intact It is easy to tear away its body and leave the mouth parts in the wound If the wound is infected, the usual principles of surgical treatment will apply In cases showing grave symptoms of respiratory embarrassment, artificial respiration may be tried or a Drinker or similar type of respirator used

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Symptomatology — In a well developed case the cardinal signs are the characteristically shaped skull exophthalmos and impairment of vision A very large number of other associated symptoms and signs have been described in various cases The skull as the various names of this condition denote is high and more or less pointed Often the excessive height is confined to the frontal region but it may be farther back in the region of what is normally the vertex In some cases extraordinary bulging of the temporal regions has occurred so that the head viewed from the anterior aspect has a more or less diamond shaped outline The mild forms have a tall dome shaped head the more severe forms a high obtusely pointed head The upper squamous portions of the temporal bones may bulge out beyond the external surfaces of the zygomata In other cases this temporal bulging is absent Acrocephaly may be considered as a typical reaction to premature synostosis of the sutures in the posterior part of the skull but there may be atypical asymmetrical reactions in which one side of the head is larger than the other etc the shape of the head varying with the site of the premature synostoses

The exophthalmos may be of any degree in some cases amounting to actual displacement of the eyeball from the orbit Harman mentions a case in which the eyes appeared to be almost dropping out so that the child had to go about with a hood over its head Carpenter reports a case in a five weeks old infant that died two weeks later in which the eyes were kept in position merely by the lids and could be dislocated readily so that they hung suspended by their muscle and nerve attachments Fletcher mentions the case of an infant who frequently was brought to Dr John Thomson of Edinburgh to have its eyes replaced in their sockets On the other hand very mild degrees of exophthalmos may occur or it may be absent There may be considerable difference in the degree of the protrusion of the two eyes in some cases The ears appear to be low on the head because of the height of the cranium Many patients are mouth breathers and have a vacant stupid expression Dental anomalies and early caries of the teeth are frequent

Visual defects are exceedingly common in acrocephaly Among Brav s 77 collected cases only one had normal vision in both eyes with correcting lenses most had serious visual defects in one or both eyes many were blind or practically so High grade myopia is very frequent Other common associated ocular defects are divergent strabismus and nystagmus The last usually is lateral and of a very fine character sometimes being so fine that it is detected most readily during ophthalmoscopic examination the movements making examination of the fundi difficult In addition to these factors Dodd and McMullan describe in their case

times of the most extreme degree divergent strabismus and nystagmus

History —According to Bertolotti Oribasius described the acrocephalic syndrome about 1 600 years ago Virchow published an account of it in 1856 During the next few decades a number of other reports appeared in the German literature The first record in English known to the present author is that of Friedenwald of Baltimore in 1893 Since then a very considerable literature has grown up on the subject most of it being in ophthalmological journals however, so that it is hardly as familiar to internists and general practitioners as it should be For this reason it is included in this chapter on Unusual Diseases etc. though in reality it is hardly unusual Patry writes that the skulls of Walter Scott Paracelsus, William Humboldt Mechel and other exceptionally intelligent men had mild acrocephaly The most exhaustive treatise on acrocephaly to date is probably that of Hans Gunther in 1931

Etiology —Little is known regarding the etiology of this condition beyond what Virchow stated in his original contribution viz that it is due to a premature synostosis of certain sutures in the skull limiting the growth of the brain and head in certain regions and causing disproportionate compensatory growth especially in the region of the anterior fontanelle or in front of this The cause of the premature synostosis is unknown In severe cases excessive intracranial pressure is produced and this is an important factor in causing a number of the associated symptoms such as defective vision and exophthalmos Constriction of the optic nerves by narrowed optic foramina also has been thought to be a factor in producing visual defects in some cases Acrocephaly has been reported at almost all ages but much more frequently in childhood and youth In 1912 Brav analyzed a series of 77 cases collected from the literature and found that in the cases reported in which the age was given (56 cases) it ranged from 4 months to 63 years the majority (46 cases) being under 21 Of 46 cases 39 were males and 9 females. Fletcher and also Davis finds that race has no influence in etiology Syphilis and rickets are not factors Heredity appears to be a factor in some cases Stephenson notes the cases of a mother and two children who were affected in a family of five Schmidt has reported cases in a mother and child Irion reports four cases in three generations Engerth cases in identical twins Sawhney in two brothers and a number of others report cases in siblings in the recent literature According to Fletcher, a few cases have seemed to date from a blow or a fall on the head

Pathology —In its grosser and more obvious aspects this constitutes part and parcel of the symptomatology and will be discussed under that heading Roentgenological study furnishes further data of importance

2 Those in whom the characteristic changes in the head develop during the first few months of life In these it is usual to find gradually increasing impairment of vision Ability to read ordinary type is unusual in adults

3 Cases in which the characteristic changes begin somewhere from the second to the sixth year In these an increasing visual defect often is the first symptom noted

Fletcher's article is notable for its excellent clinical and pathological illustrations

Diagnosis —Usually this is obvious on inspection The roentgenological findings are of special interest in differentiating simple acrocephaly from brain tumor There is convolutional atrophy of the skull so that in a good film one can actually visualize to a degree in an advanced case the cerebral convolutions This convolutional atrophy may appear as a coarse network in the cranium most marked in the frontal region and *much more marked than ever is found in a normal skull* *In extreme* cases one can see also especially in lateral films that the brain appears to be crowded and more or less pressed out of its normal shape The frontal and antral sinuses often are rudimentary or absent Frequently the sella is unusually clear enlarged and displaced backwards but it is never eroded The articles of Dwyer and of Davis contain especially fine roentgenological illustrations The present author has found no record of encephalographic or ventriculographic studies in acrocephaly but it is reasonable to suppose that such studies would show certain distortions especially in extreme cases

Dock calls attention to one pitfall that may cause an unwary observer to miss the diagnosis and that is the presence of certain types of arrangement of women's hair which may mask the otherwise obvious cranial abnormality

Prognosis —There seems little evidence that acrocephaly per se shortens life although the oldest case encountered by the present author in the literature was 63 When blindness is present the usual hazards of that condition are present and of course excessive intracranial pressure will kill if not relieved

Prophylaxis and Treatment —No effective prophylaxis is known Much has been written about the use of various endocrine products in treatment but no such method has yet proved of definite value The best opinion today favors early surgical decompression and before the dura is opened in this procedure it is advised that ventricular puncture be done drawing off from 10 to 50 c c of fluid In some cases operation seems to do no good In others it has given brilliant relief In some death has followed

white optic discs with well defined margins the foramina of the lamina cribrosa not being visible The veins were rather tortuous and the appearance suggestive of postneuritic atrophy Their patient s vision was fair as he could count fingers at six meters with each eye More exact determination was impossible because of defective intelligence Postneuritic atrophy is the most frequent abnormality seen in the fundi though a few cases have been observed early enough to show optic neuritis with choked discs developing atrophy later Dodd and McMullan state that one case has been reported with acute optic neuritis with subsequent complete recovery from the neuritis and restoration of sight Stood reported a case showing normal fundi but with total blindness ascribed to defective development of the occipital lobes

Headache is very common and may be very severe It may be general or localized in various regions Vertigo is less frequent and convulsions are relatively uncommon though they may occur, especially in infancy and childhood

Usually the intelligence is normal but all grades of mentality from idiocy to brilliance have been noted

A number of additional peculiarities in the skull have been described, but these are inconstant When a hooked nose heavy lower lip prognathous mandible and high arched palate all are associated and the forehead is extremely prominent the condition is termed craniofacial dysostosis or Crouzon s disease as described elsewhere in this chapter Bertolotti would group a number of abnormalities affecting the skull under the term pathological craniosynostosis

A great variety of abnormalities in the body outside of the head has been described in association with acrocephaly Perhaps the best known of such is syndactylism the combination being known as acrocephalosyndactylism or Apert s syndrome described elsewhere in this chapter When a massive skeleton is associated along with certain phalangeal deformities the condition is called dystrophia periostalis hyperplastica familiaris or Dzierzynsky s syndrome also described elsewhere in this chapter Other associated conditions are bilateral subluxation of the head of the radius on extension and supination of the forearm without impairment of function probably due to lax ligaments large knee joints with genu valgum various malformations of the elbows and shoulder joints dwarfism hemolytic jaundice essential polycythemia erythroblastic anemia

Fletcher recognizes three groups of cases as follows

1 Those in whom exophthalmos and the characteristic head deformity are present definitely at birth In these cases total blindness is frequent This group forms a small proportion of the total cases

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Dystrophia Periostalis Hyperplastica Familiaris

Synonym — Dzierzynsky's syndrome

Definition — A familial developmental dysfunction characterized by a massive skeleton a high narrow pointed head premature closing of the fontanelles and sutures of the skull and certain deformities of the phalanges In some cases the skull is normal and only the phalanges are affected in others the skull alone is involved

So far as is known to the present author only one paper dealing with this condition is to be found in the literature viz a contribution by Dzierzynsky published in 1913 in which he describes 12 cases 8 males and 4 females in the second and third generations of a family of farmers Inheritance occurred through both the male and female At the time of the report none in the third generation had had children

Symptomatology and Diagnosis — The deformities include a high head narrowed in its upper portion especially from the side so that the vault

soon from meningitis or pneumonia Faber and Towne advise craniectomy in the first six months in the congenital cases to prevent blindness removing ample strips of the calvarium They consider even this of little use after the age of two years

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HELMHOLZ H F and HARRINGTON E R A syndrome characterized by

Gargoylism

Synonyms — Hurler's syndrome, Hurler's disease

Definition — A bizarre syndrome consisting of extensive skeletal deformities, cloudiness of both corneae, mental deficiency and enlargement of the liver and spleen and in some cases infiltration of cells with a lipid substance. Additional features such as *hernias* described in some cases are not essential to the diagnosis. Various incomplete types also have been reported. Ophthalmological literature is full of reports of congenital clouding of the corneae but without any of the other factors mentioned this hardly can be considered as incomplete gargoylism.

History — In 1919 Gertrud Hurler reported a typical case complicated with bilateral hernia. A number of incomplete cases were reported within the next five years. The first report in English of a fully developed case which the present author has found is that of Putnam and Pelkan in 1925. In 1931 Helmholz and Harrington reviewed a number of cases including some of their own. In 1934 Sheldon and also Poynton, Lightwood and Ellis presented cases and discussed the subject before the Royal Society of Medicine of London. In 1936 Ellis, Sheldon and Capon described seven cases and gave the syndrome the name gargoylism, the previous cases having been reported merely as bizarre combinations of striking abnormalities without attaching any specific name to the syndrome. In 1938 Ellis and also Slot and Burgess presented further cases before the Royal Society of Medicine, and Kressler and Aegerter published an article that is of special interest from the standpoint of their roentgenological illustrations; they summarize reports on 59 cases.

Etiology — This is unknown. Most of the cases reported are isolated ones but there are at least two reports in the literature describing cases in two siblings. The condition may be considered as an "inborn error of metabolism" but is not known definitely to be familial although Cockayne thinks it may be a double recessive inheritable condition. In general the family histories of the patients reported have been normal and syphilis has been excluded. Myxedema is not present in these patients. Consanguinity of parents has not been a factor. Kressler and Aegerter find that the brain in gargoylism is comparable to that seen in both amaurotic family idiocy and the Niemann-Pick disease. They believe that the most likely cause of gargoylism probably is a metabolic dysfunction of a complex lipid and suggest that infiltration of this material into the liver, spleen, heart, lymph nodes, corneae, pituitary and possibly other endocrine glands may account for many of the outstanding symptoms and signs, thus placing it in the group of lipoidosis or xantho-

of the cranium is wedge shaped The vault of the cranium is crowned by a sharply projecting crest along the sagittal suture and from the ends of this the skull slopes very sharply both before and behind The frontal bone is excessively high All the facial bones are prominent especially the nasal bones which are extremely large The orbits are small The maxilla and upper teeth are prominent though many teeth are lacking The palate and ears are normal the spine is not deformed There is a marked bowing in the middle of the sternum, the upper sternum being arched forward the lower parallel to the spine The ribs flare out excessively from the sternum especially in the upper part The phalangeal changes consist of thickening with or without limitation of movement in the interphalangeal joints

X ray changes include a very deep cranial fossa the cranial and facial bones being much thickened and sclerosed especially the inner table of the vault of the skull The orbits are short

Dzierzynsky considers this syndrome as the antithesis of the cleido cranial dysostosis described by Marie and Sainton discussed elsewhere in this chapter He calls the latter dystrophia periostalis hypoplastica familiaris and contrasts the two conditions as follows

Dystrophia Periostalis Hypoplastica Familiaris (*Cleidocranial Dysostosis*)	*Dystrophia Periostalis Hyperplastica Familiaris* (*Dzierzynsky s Syndrome*)
Fontanelles open a long time	Fontanelles close early
Wide sutures and many extra ones	Premature closing of sutures
Thinning of cranial vault	Thickening of cranial vault
Hydrocephalic head	High narrow pointed head
Kyphosis of base of skull	Lordosis of base of skull
Face even nose sunk in	Face and nose projecting
Short stature	Normal height
Clavicles absent or rudimentary	Clavicles thickened
Fully developed medullary canal in long bones	Massive skeleton Thickened long and short bones

The diagnosis is made on inspection Additional details are ascertained by roentgenological study The condition naturally is permanent and no prophylactic or therapeutic measures are of avail

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present in the cerebellum and in the frontal and parietal lobes it is difficult to say how much this complicating tuberculosis determined the pathology Most of the cases reported have shown no association with tuberculosis

Symptomatology — In its complete form gargoylism exhibits an abnormally shaped head usually of scaphocephalic type lumbar or thoracicolumbar kyphosis short thick extremities with limited movements at the joints especially on extension tending to involve the upper extremities more than the lower and sometimes exhibiting clawlike hands and feet a bilateral clouding of the cornea a considerable degree of mental deficiency and enlargement of the liver and spleen the latter being noted in 11 of 19 cases collected by Kressler and Aegerter Often there is a shortening of the cervical spine so that the rather massive head seems to rest directly on the shoulders Heavy thick clavicles have been reported as has pigeon breast but the changes in the thoracic cage are less marked than is usually the case in Morquio s disease with which it has been confounded The long bones of the extremities tend to be thicker and shorter than normal There is limitation of movement in the joints of the extremities most marked in the interphalangeal articulations The hands are broad and pawlike and the short clumsy fingers usually show some degree of flexion with definite claw hands in advanced cases as noted above In Ashby Stewart and Watkin s cases the thumbs and metacarpophalangeal joints showed no limitation of movement The teeth often are very irregular and may be widely spaced The tongue may be large and protruding and show fissures The skin of the face may appear normal but that of the body pale sallow and dry with loss of elasticity so that it can be lifted in folds Cushions of fat may develop in the breasts and abdomen A number of cases have shown persistent lanugo a few hypertrichosis Both liver and spleen may be enlarged the liver may be enlarged without the spleen being enlarged or as already noted neither organ may be enlarged as shown in 5 of 19 cases (Kressler and Aegerter) Umbilical or inguinal hernia may complicate the picture Most of the patients have been low grade imbeciles Ellis and Capon s female dwarf of 18 was the most intelligent case thus far described She could speak a few words understand simple requests and she had acquired clean habits Mental regression has been observed e g one of Ashby Stewart and Watkin s patients was clean in habits and could speak at 5½ years of age but 15 years later had sunk to complete amentia Most of the patients reported have been friendly and docile The formed elements of the blood are normal Sexual development may be infantile or proportional to the physical development Hydrocephalus may occur

matosis diseases The skeletal signs however remain unexplained by this hypothesis as the bone marrow in their cases showed no infiltration and they attribute these signs to a defect in the germ plasm

Helmholz and Harrington recognize seven types of abnormalities in which cranial dysostosis is an outstanding feature as follows (1) oxycephaly described by Virchow in 1856 (2) hereditary cleidocranial dysostosis of Marie and Sainton (1898) (3) acrocephalosyndactyly (Apert 1906) (4) hereditary craniofacial dysostosis (Crouzon 1912), (5) dystrophia periostalis hyperplastica familiaris (Dzierzynsky 1913) (6) hypertelorism (Creig 1924) (7) the condition now under discussion The first six of these have been described already in this chapter While there are certain points of similarity among them there are many points of difference and there is no convincing evidence of any definite etiologic relationship between gargoylism and any of the others

Pathology — Grossly the skeletal changes and the usual enlargement of liver and spleen are obvious and striking on inspection and will be described further under Symptomatology Ashby Stewart and Watkin performed necropsies on two incomplete cases lacking hepato pleno megaly In both they found a large persistent thymus There were no foam cells in the liver and spleen but as stated those organs were not enlarged In every part of the nervous system in both cases the ganglion cells showed a striking alteration the cytoplasm being distended by the deposit of an abnormal substance and the Nissl granules reduced in number and crowded to one side but the cell processes little affected Chemical analysis in one case showed a marked reduction in cerebrosides in the cerebral cortex but not in the white matter Lipid deposits were found around many of the blood vessels in the brain so these authorities consider that gargoylism is a disturbance in lipid metabolism despite their failure to find foam cells

At autopsy on one case Kressler and Aegerter found changes in the skeletal system hepato splenomegaly lesions in the central nervous system and corneal cloudiness Microscopical examination showed heart muscle fibres swollen misshapen and vacuolated cells in liver spleen and lymph nodes showed vacuoles Cells in the pituitary especially the chromophobe cells were vacuolated Nerve cells showed lipid material and degenerative changes of the Nissl bodies They believed that there was present infiltration extensively of body cells with one of the complex lipids analogous to findings in the xanthomatoses but whose chemical nature they did not determine

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In Hurler s case there were edema of the brain and internal hydrocephalus with atrophy of the temporal lobes but as tuberculomas were

gested multiple areas of cortical atrophy with the greatest involvement in the frontal region

Diagnosis — This is obvious in fully developed typical cases The skull is more affected than in Morquio s disease and the marked pigeon breast seen in the latter is less marked or absent in gargoylism The appearance of the thoracic cage strongly suggests rickets However the associated conditions outside the skeleton i e the cloudy corneæ mental deficiency and hepato splenomegaly should prevent any confusion with other diseases

Prognosis — Most cases die early of intercurrent infections The oldest case thus far reported that is known to the present author is that of Ellis s 18 year old girl No effective *prophylaxis* or *treatment* is known Thyroid extract has been tried therapeutically and found wanting

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No abnormality of the thyroid thymus or lymph nodes has been reported during life The heart and lungs are normal, and no urinary abnormality has been reported

As Putnam and Pelkan s description is one of the best in the litera ture it is worthy of note representing as it does, a fully developed case The patient was a 17 months old girl with a normal family history who appeared normal at birth She was breast fed for 11 months Her de velopment seemed abnormal from the age of 11 months until the time of her admission to the Children s Hospital in Boston six months later when she could say only Mama and Daddy She happened to have an upper respiratory infection with a discharging ear on admission but this cleared up rapidly She seemed apathetic much of the time and fell asleep easily but resented efforts at physical examination She had a marked thoracicolumbar kyphosis a flaring costal margin some beading of the ribs a Harrison s groove and a pot belly Her muscles were poorly developed and flabby and there was considerable lanugo over the upper part of the trunk Her head was scaphocephalic and conspicuously long anteroposteriorly with a very prominent forehead which gave a concave profile to her face The anterior fontanelle was open and measured 4 × 4 cm Her ears were very low on her head There was a slight diffuse clouding of both corneæ but no evidence of inflammation in the eyes The jaw was broad and heavy the palate very narrow and short but not high The heart and lungs were normal The arms were very short and thick The abdomen was soft and bulging but there were no herniæ The spleen was easily palpable and the liver greatly enlarged This patient did not have abnormally short legs as a number of others reported have had There were however large folds of tissue over the inner aspects of the thighs Numerous laboratory studies all were nega tive X ray showed the bones to be denser than normal with a heavy squared appearance especially in the long bones There were heavy coarse trabeculations in the small bones of the hands and feet The skull was rather large with aberrant vessels in both frontal areas

This description by Putnam and Pelkan may be considered typical Certain variations and additional details remain to be noted Instead of the usual scaphocephaly there may be acrocephaly or brachycephaly An enlarged sella has been reported in some cases but no erosion found The supraorbital ridges may be excessively prominent and bony ridges or exostoses may appear in various parts of the skull The corneal opacities may be spotty rather than diffuse Very recently (1938) Ellis has reported that in one case an encephalogram made after injecting 50 c c of air showed a generalized dilatation of the ventricles and also sug

CHAPTER XLIII-B

UNUSUAL DISEASES AND SYMPTOM-COMPLEXES NOT DISCUSSED IN OTHER CHAPTERS (Continued)

By FREDERICK R TAYLOR

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ACROMICRIA

Synonyms — Dystrophia osteo genitalis acrosclerosis The last two are given by Barsony but seem undesirable terms from the descriptions given of this disease and the frequent use of the second term in an entirely different meaning

Definition — A condition characterized by abnormally small hands and feet which tend to be cyanotic and small facial bones It may or may not be associated with obesity and genital hypoplasia or with dwarfism One reported case was associated with diabetes insipidus It may be considered as the antithesis of acromegaly

History — The earliest paper which the present author has seen in which the term acromicria is used and in which its antithetical relationship to acromegaly was recognized is that by Brugsch in 1927 The available literature on the subject under this name is scanty

Etiology and Pathology — The condition is believed to be due to either an aplasia or a functional deficiency of the anterior lobe of the hypophysis The present writer has not found any record of a necropsy in a case of acromicria so can say nothing about any pathological changes other than those which can be observed by clinical methods and these will be discussed under Symptomatology

slight limitation of the visual fields The final diagnosis was a functional insufficiency of the anterior hypophysis

The last case to be mentioned is that of Decourt and Trotot a woman aged 39 years who was short fat and showed acromicria Her blood Wasserman reaction was negative blood counts normal and blood chemistry essentially normal though her fasting blood sugar while within normal limits was unusually variable ranging from 76 to 100 mgm per cent and a glucose tolerance test showed a prolonged and exaggerated reaction She began to menstruate at the age of 7 years and at 9 showed an enlarged abdomen which was found to be due to an ovarian cyst which was removed Her periods were normal at the age of 13 She became pregnant at 25 and gave birth to a baby with Little s disease Four years later she had a 2½ months abortion At 27 she developed menorrhagia from a fibroid tumor and had a total hysterectomy Her secondary sex characters were normal She had three sisters of normal growth The authors point out that this patient had a number of unrelated conditions The acromicria could not be ascribed to the ovarian cyst or to the fibroid but must be considered as the result of a pituitary disturbance opposite in nature to that occurring in acromegaly

Diagnosis is obvious on inspection

Prognosis — Barsony states that spontaneous recovery has occurred

Treatment — Various pituitary preparations have been tried as have certain other endocrine products but it is not certain that they have produced any favorable results

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March 1 1940

Leontiasis Ossea

Synonyms — Hyperostosis cranii craniosclerosis megalocephaly ophthalomegaly

Symptomatology — The literature available to this author is so scanty that a brief summary of the few articles he has seen seems in order Brugsch s patient was a 23 year old woman 157 cm tall (about 5 ft 3 in) who weighed 47 kg (103 4 lbs) She was healthy till the age of 13 when she developed a tuberculous infection in her eyes which later became arrested This was followed by profuse menstruation but at the age of 20 the patient developed complete amenorrhea diabetes insipidus appeared with an output of 8 to 10 liters of urine daily a tuberculous process lit up in the left eye and it was noted that her fingers and toes were small and cyanotic The spleen was enlarged but this presumably was coincident with rather than an integral part of her acromicria as was the tuberculosis X ray showed a small sella and a loss of calcium in the bones Brugsch considered the acromicria to be due to an aplasia of the anterior lobe of the hypophysis

Barsony especially points out the contrast between acromegaly and acromicria In the latter condition he notes hypoplasia of the soft parts of the face thinning and shortening of the facial cartilages thin small nose and narrow lips so that the teeth often show between them receding chin thinned eyebrows sunken malar bones and mask face' appearance and notes that the patient s profile resembles that of a bird He calls attention to the thin partly absorbed bones of the hands and feet and the very small fingers and toes

Carnot and Cachera report the case of a 30 year old married woman 141 cm tall (about 4 ft 8½ in) Her head and trunk were normal in size Her face looked rather old for her age Her teeth were defective but suggested a dystrophy rather than acquired defects Her bony thorax abdomen and pelvis were normally developed Her extremities contrasted strongly with her trunk and head Adipose in their proximal parts in their distal portions they were strikingly small Her arms forearms thighs and legs were of about normal length but her hands and feet were very small her hands resembling those of a 10 year old girl She was well proportioned and not fat Her fingers were thin and short The skin was normal except for some acrocyanosis The feet showed intense submalleolar cyanosis and were cold There was no evidence of infantilism the secondary sexual characters being well marked Menstruation began at 13 and was normal at first At the age of 18 her periods became scanty and infrequent At 22 she became pregnant but aborted at 3 months A year later she bore an apparently normal baby that died of undetermined cause in three weeks At 27 she developed complete amenorrhea and showed marked obesity especially of the abdomen A year later she developed severe left temporal headaches and hypotension with

with exostoses etc Marked involvement of the soft tissues or caries of the bone are not recognized generally as manifestations of leontiasis ossea Kanavel says that some consider the condition as a localized acromegaly Ruppe recognizes two types roentgenologically both showing a fibrous osteopathy but one associated with the production of osteoid tissue and the other with areas of necrosis and calcification Friedman finds the histology to be of two types one appearing identical with that of Paget s disease and the other with that of von Recklinghausen s osteitis fibrosa Gemmell says that leontiasis ossea shows a more profound hyperostosis of the skull than does Paget s disease and states that cases occur without the clinical or roentgenological characteristics of either Paget s or von Recklinghausen s disease He adds that many atypical cases suggest the associated lesions of the two latter conditions but notes that there are innumerable cases of Paget s disease without evidence of leontiasis ossea and concludes that the latter condition remains a clinical and roentgenologic entity Marx believes that it has a characteristic histological picture but there is no general agreement on this point

Symptomatology —The disease usually begins in the bones of the face and extends to the cranium Such extension may never occur however or the process may start in the cranium and involve the face later Usually it is painless When the facial bones are affected extensively the face has a leonine appearance from which the syndrome derives its name Practically the entire skull may be involved or any part thereof but the process does not affect other parts of the body Many cases have been reported in the literature as leontiasis ossea in which other parts of the body have been affected but the present writer regards such cases as either mistaken diagnoses or in a few instances as the coincidental association of some other disease with leontiasis Many cases have been noted in children and even congenital cases have been described Hale White s patient a 32 year old carpenter was of stunted growth being only 4 ft 10 in tall He had a very prominent ridge of bone running around his head horizontally displacing his ears downwards The bones of his face were unaffected A photograph taken at the age of 5 years showed that the deformity of his head was present then

Putnam listed a formidable variety of symptoms and signs including thickening of the bones of the head exophthalmos deafness blindness facial paralysis headache double optic neuritis suppuration in the ears and elsewhere epileptic attacks (sometimes very early in the disease) vertigo a peculiar giving way of the legs disturbance of respiration interference with mastication loss of teeth drowsiness and mental deterioration Not all of these symptoms are present in one case

Definition — Leontiasis ossea is a symptom complex characterized by enlargement of some or all of the bones of the skull the facial bones being affected most frequently A number of different types have been described including a type indistinguishable from a localized form of Paget s disease (osteitis deformans) Whether it is ever a distinct clinical entity or whether it is always merely a localized facial or craniofacial manifestation of certain skeletal diseases that usually are not limited to the head, is still a subject for debate Hamburger and Nichlas consider that the term leontiasis ossea is useful still as descriptive of hyperostosis of unknown origin in the skull though they grant that many cases so designated may be cases of Paget s disease that eventually will show involvement of other parts of the skeleton Other cases have proved to be examples of von Recklinghausen s osteitis fibrosa cystica (hyperparathyroidism)

History — Hodgson states that leontiasis ossea was described first by Malpighi in *Opera Posthuma* in 1700 Comby says that Virchow gave the condition its present name in 1877 W Hale White in reporting a case states that Virchow s cases were of a different type from his showing as they did involvement of the orbits local bony development and often, mental symptoms or headache Baumgarten published a monograph on leontiasis ossea in Paris in 1892

Etiology — Any consideration of the etiology of this syndrome naturally must depend on whether it is thought of as a definite entity or not Ager considered it due to a pituitary disturbance and reported a unique case associated with intense thirst and polyuria In most cases however the etiology is far from clear even if the condition be looked upon as a clinico pathological entity

Pathology — In a syndrome concerning the nature of which there is so much difference of opinion conceptions regarding the pathology naturally will vary too Knaggs recognizes four types (1) a creeping periostitis (2) a diffuse osteitis fibrosa of the bones of the face and skull which he thinks may represent a partial form of Paget s disease (3) a circumscribed osteitis of one or more cranial bones (4) an osteitis beginning in one or both jaws but rarely spreading beyond them His discussion of the whole subject is perhaps the most exhaustive in the literature Hodgson s classification practically agrees with that of Knaggs He states that Pierre Marie and Paget considered osteitis deformans as distinct from leontiasis ossea whereas Bockenheimer Schmidt Bost Lorch and Prince believed the two conditions identical White states that many different conditions have been described under the name of leontiasis ossea some having both the soft tissues and bones affected some with caries some

with exostoses etc Marked involvement of the soft tissues or caries of the bone are not recognized generally as manifestations of leontiasis ossea Kummel says that some consider the condition as a localized acromegaly Ruppe recognizes two types roentgenologically both showing a fibrous osteopathy but one associated with the production of osteoid tissue and the other with areas of necrosis and calcification Friedman finds the histology to be of two types one appearing identical with that of Paget s disease and the other with that of von Recklinghausen s osteitis fibrosa Gemmell says that leontiasis ossea shows a more profound hyperostosis of the skull than does Paget s disease and states that cases occur without the clinical or roentgenological characteristics of either Paget s or von Recklinghausen s disease He adds that many atypical cases suggest the associated lesions of the two latter conditions but notes that there are innumerable cases of Paget s disease without evidence of leontiasis ossea and concludes that the latter condition remains a clinical and roentgenologic entity Marx believes that it has a characteristic histological picture but there is no general agreement on this point

Symptomatology — The disease usually begins in the bones of the face and extends to the cranium Such extension may never occur however or the process may start in the cranium and involve the face later Usually it is painless When the facial bones are affected extensively the face has a leonine appearance from which the syndrome derives its name Practically the entire skull may be involved or any part thereof but the process does not affect other parts of the body Many cases have been reported in the literature as leontiasis ossea in which other parts of the body have been affected but the present writer regards such cases as either mistaken diagnoses or in a few instances as the coincidental association of some other disease with leontiasis Many cases have been noted in children and even congenital cases have been described Hale White s patient a 32 year old carpenter was of stunted growth being only 4 ft 10 in tall He had a very prominent ridge of bone running around his head horizontally displacing his ears downwards The bones of his face were unaffected A photograph taken at the age of 5 years showed that the deformity of his head was present then

Putnam listed a formidable variety of symptoms and signs including thickening of the bones of the head exophthalmos deafness blindness facial paralysis headache double optic neuritis suppuration in the ears and elsewhere epileptic attacks (sometimes very early in the disease) vertigo a peculiar giving way of the legs disturbance of respiration interference with mastication loss of teeth drowsiness and mental deterioration Not all of these symptoms are present in one case

Mix's patient, a 32 year old woman, noted in her 17th year a swelling at the inner corner of her left eye. Later, other swellings appeared in the bones of the upper part of her face, especially in the orbital plates of the frontal bones and about the supraorbital ridges. The nasal process of the right maxilla became enlarged, too, and the malar and parietal bones were involved extensively, so that the head became roughly triangular in its anterior aspect, the chin forming the apex and the frontal bones the base thereof. Hypertelorism also developed. There was also very marked exophthalmos, the eyes being half way out of their sockets. The bony growth was slow but steady. The sense of smell had been absent for years but was present at the time of examination. For some time the patient had been unable to sneeze but this power had returned. There were no disturbances of vision. There was some headache but not of a type to suggest increased intracranial pressure. There was no evidence of cortical irritation. The soft tissues were not affected.

Ager's patient was a boy of six years who at the age of 3½ years developed intense thirst, polyuria, colitis, vomiting, chills, fever and at times spinal rigidity. At the age of 5 a marked bulge was noted in his right upper cheek. X-rays showed this to be due to thickening of the right malar bone. His eyes were normal. Apert and Bordet's patient, a 9 year old boy, had both maxillæ greatly enlarged. His Wassermann reaction was negative. Apert and Garcian reported a congenital case in a girl aged 11 months, also with a negative Wassermann reaction. The alveolar edges of her mouth were much enlarged and the face was massive.

DeMassary and Richet reported a case in a woman of 63 who had an enormous cranium and large maxillæ but a small chin, so that her face looked like that of a baby. X-ray showed a thick ragged looking skull. DeMassary and Boquien reported a necropsy on this same patient and found the skull enormously thickened and very similar to, if not identical with, the skull of Paget's disease. In Capon's patient the frontal bones were affected particularly. In Gill's patient, an 18 year old boy, the condition developed about 4 months after a series of facial traumata. Clark recognizes three clinical types: (1) cases in which the entire head is affected, (2) cases in which only the middle and lower face are affected and (3) cases in which only the mandible is involved. He notes that the process usually starts in a maxilla, and that in extreme cases the head may weigh eight times as much as normal. He states that compression of the brain may be fatal.

Diagnosis. — It is questionable whether leontiasis ossea can be differentiated from *Paget's disease* that is limited to the skull except by the

x ray which is quite characteristic Usually however the latter condition eventually affects other parts of the skeleton *Osteitis fibrosa cystica* should be differentiated by its roentgenologic picture and by other evidences of hyperparathyroidism This too usually involves other bones outside the skull *Acromegaly* shows enlargement of the hands and feet involvement of the soft parts and abnormally large sella etc Sherwood Moore s disease (metabolic craniopathy calvarial hyperostosis) shows marked thickening of the calvarium localized or diffuse often with increased density of the diploe but does not present the gross enlargement and leonine facies seen in leontiasis ossea The facial bones are not affected in metabolic craniopathy and there is nearly always associated obesity in that condition

Nodular leprosy while it may produce a leonine facies should cause no confusion for the extensive involvement of the skin evidences of leprosy elsewhere in the body etc give a totally different picture The most important condition to differentiate is that of a *malignant tumor* arising in a facial or cranial bone A rapidly growing painful asymmetrical lesion favors malignancy but at times leontiasis may show pain and rapid growth Usually some inflammatory reaction and edema may be seen in the soft tissue overlying malignancy in the bones but too much reliance should not be placed on their absence

Roentgenological studies may give important aid by showing bone destruction in tumor but they are not always infallible Pilcher and Hilton in 1936 reported a case believed to be leontiasis until biopsy showed it to be a diffuse carcinomatous infiltration of the facial and cranial bones In all doubtful cases biopsy must be resorted to as the final arbiter to exclude or establish the diagnosis of malignancy

A *benign osteoma* may give much difficulty in the early stages Clark s patient had been operated on for a supposed osteoma of the lower jaw but the subsequent spread of the process revealed the true diagnosis

Prognosis —The disease may be fatal after many years usually from increased intracranial pressure The outlook is better in cases confined to the facial bones and best in those limited to the mandible The more rapid the spread of the process the worse is the prognosis Many cases develop so slowly that they do not cause serious trouble though the condition is incurable Gill states that the disease usually lasts from 20 to 30 years

Treatment is of no avail except for the fact that in certain cases operation may give temporary relief from pressure symptoms

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March 1 1940

HEMIATROPHY

Synonyms — Progressive hemiatrophy progressive unilateral atrophy neurotic atrophy of the face (Virchow) facial trophoneurosis (Romberg)

prosopodismorphia (Bergson) atrophy of the connective tissue of the face or lacunar aplasia (Lande)

Definition — *Progressive unilateral atrophy is a condition of unknown* etiology which shows no evidence as a rule of involvement of the motor pathways in the nervous system and is characterized by a progressive wasting of the skin connective tissue subcutaneous fat and bone of one side of the body Very rarely the muscles may be affected to some degree An entire half of the body may be involved in which case the hemiatrophy is said to be total or more frequently limited to some part of *one side of the body when it is said to be partial Either side may be* affected Very rarely a crossed hemiatrophy has been observed e g atrophy of one side of the face and of the opposite side of the rest of the body Occasionally the upper portion of the body may be involved (wasting of face neck arms thorax) leaving the lower portion unaffected

History — According to Eulenburg Parry described facial hemiatrophy *in 1825 Lasègue states that Carswell first arranged scientifically the* various lesions that might occur in this condition In 1895 Marie and Marinesco described a case involving the face and upper extremity complicated by a facial paralysis all on the same side Burrell states that Paul Broca described a case of total hemiatrophy in 1859 According to Meyer Romberg originated the term facial hemiatrophy Archambault and Fromm in 1932 gave the most complete discussion of the subject *thus far to be found in the literature*

Etiology — This is unknown Congenital cases have been reported but are rare This is in contradistinction to hemihypertrophy to be described later in which congenital cases are the rule In 37 cases collected from the literature by the writer the history of onset i e of the time when the discrepancy in the two sides was noted first was in the age period 0 to 10 years in 11 cases from 11 to 20 years in 19 cases from 21 to 30 years in 5 cases and over 30 years in 2 cases Among 33 cases it was twice as common in females 22 being of that sex and 11 males A few *cases have followed shortly after trauma to the side of the face involved* but most cases have no such history Fuller reports a facial case following a radical antrum operation on the same side but is unable to explain the relationship to the operation if any Syphilis is not a factor

Incidence — Once considered one of the rarest of abnormalities Archambault and Fromm in 1932 collected 400 cases from the literature 24 of which were examples of total hemiatrophy To these 24 Finesilver and Rosow added 10 more cases in 1938 making a total of at least 34 cases of total hemiatrophy on record

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Pathology — Those features of the pathology which are discernible by clinical methods such as physical examination and roentgenology will be mentioned elsewhere Frequently but by no means always patches in the skin may appear at the onset of the disease, the histology of which is indistinguishable from that of localized scleroderma (morphoea) Because of the unilateral or in rare cases crossed type of involvement search for pathological changes naturally has been made in the nervous system but despite arguments on behalf of peripheral (trigeminal) nerve involvement nuclear sympathetic ependymal or other localization we have no definite knowledge of the primary seat of the disease Referred to as a 'tropho neurosis by many this throws no real light on the subject As stated already both the soft tissues and bones are affected but as a rule to which there are few exceptions the muscles are relatively or absolutely exempt There may be almost complete disappearance of the subcutaneous fat There has been considerable discussion as to the possible identity of hemiatrophy and scleroderma but many cases of hemiatrophy fail to show areas of scleroderma and many cases of scleroderma do not show hemiatrophy Claude and Sezary report a facial case showing lymphocytosis of the spinal fluid Burrell reports a case associated with atrophy of the right cerebral hemisphere and left side of the cerebellum in an insane patient Kempmeier reports a case of total hemiatrophy associated with a large spongioblastoma originating almost directly in the central part of the cerebellum

Symptomatology — Usually the condition is painless A number of cases however have been ushered in with various types of pain in the distribution of the nerve supply of the region of onset especially in the trigeminal area The pain has been described as burning stinging neuralgic toothache etc It usually clears up after a few months despite progression of the atrophy Orbison describes an extraordinary case in which atrophy was preceded for about 12 years by sensations as if the patient were having electric shocks throughout the left side of his body accompanied by dizziness These began at the age of 7 years No muscular contractions could be seen during these shocks The patient would be slightly dazed for a few moments after every attack but retained consciousness and could converse throughout the attack All the attacks were practically identical in nature They kept recurring after the onset of the atrophy

Not only may scleroderma like patches develop in the skin of the affected part at onset but erythematous patches later turning brown areas of vitiligo etc have been described In a case of the writer s erythematous patches appeared with a typical zoster like distribution from the

lumbar spine over the crest of the right ilium to the midline Often the skin looks mottled The skin lesions progress for a time and then may be come stationary Often this is true of the entire disease process The hair may fall out extensively in affected areas or may change its color

In a well developed case the atrophy of the soft parts is obvious on inspection In facial involvement the mouth may or may not be drawn to one side True facial paralysis is very rare though it has been re ported Shumway describes a remarkable case associated with recurring attacks of facial palsy some of which were preceded by pain and enoph thalmos on the affected side Kalt describes a case in which there was decrease in the size of the eyeball central disseminated choroiditis soften ing of the vitreous and opacities in the lens of the eye on the atrophic side of a facial case

The striking finding of course is the asymmetry in the two sides of the body in those parts in which one side is affected In facial involve ment if the two halves of the face are viewed separately they look like parts of the faces of two different persons When the tongue is involved it tends to protrude towards the atrophied side When a lower extremity is affected it becomes shorter than the normal one and naturally causes limping tilting of the pelvis and compensatory scoliosis unless measures are taken to prevent this

In a minority of cases some degree of mental defect has been associa ted A few of the reported patients have had a coincident tuberculosis When a maxilla or mandible is affected severely the crowns of the teeth therein may point outwards towards the cheek Sweating may or may not be diminished on the affected side Thomas reports a patient who had floating sensations and later epileptic convulsions and who complained of a deep itching of the right side of her face that could not be relieved by scratching Her right pupil was much larger than her left but both reacted well Wolff also reported a case with convulsions and anisocoria Donley reported another case associated with epilepsy Stevens described a case associated with prolonged superficial ulceration and fibrous anky losis of the joints

Diagnosis — Normal persons usually show very slight degrees of asym metry in the two sides of the body The chief source of confusion in cases with marked asymmetry is *hemihypertrophy* When this is present the sound side may be mistaken for hematrophy by comparison with the hypertrophied side The loss of subcutaneous fat and other tissues in hemiatrophy causes an abnormal appearance and the skin seems close to the bones It is helpful to exclude one half of the patient s body from the examiner s field of vision and look at one half at a time In this way

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Hemihypertrophy

Synonyms — Progressive hemihypertrophy hemigigantism progressive unilateral hypertrophy progressive facial hemiatrophy hemicraniosis

Definition — Hemihypertrophy is a condition usually congenital of unknown etiology not the result of any known type of infection of edema or neoplasm in which one side of the body or a part thereof is larger than the corresponding opposite side and which tends to progress until obvious deformity results It may be subdivided into total in which an entire half of the body is affected and partial in which a smaller portion is involved Some authors also classify it as true when both soft parts and bones are affected and false when the soft parts only are involved Occasionally the bones only may be affected Of the partial forms facial hemihypertrophy appears to be the most frequent

History — Léri and Sartre state that Boeck described the first case in 1836 Gesell says that Wagner reported a case in Germany in 1839 Desvouges one in France in 1856 and Adams one in England in 1858 Cohen states that in 1869 a treatise was published in which 12 cases were cited and that in 1697 LeBlanc collected reports of 78 cases Mobius reported a case in 1890 In the 20th century there are relatively few cases

one usually can distinguish between the two conditions In hemihyper trophy of course the affected side is abnormally large In doubtful cases roentgenological studies should be made and if the bones are affected as they usually are atrophy of bones will be evident in the one case and hypertrophy in the other

Prognosis — The condition is incurable Benign cases may become arrested spontaneously before very marked deformity results

Treatment — When a lower extremity is affected orthopedic treat ment is indicated to overcome the bad effects of the shortening of the limb Usually this takes the form of providing a properly built up shoe, which may have to be changed as the condition progresses Paraffin in jections have been used in the face but have not proved very satisfactory Moszkowicz advocates Fettplastik in such cases as does Litner In this procedure a semiliquid fat is injected into the atrophied areas in the same manner as paraffin This method of treatment, however does not seem to have met with wide acceptance thus far If some such method of plastic prosthesis can be developed that is harmless and effective in over coming the deformity and that gives reasonably permanent results it would seem to be indicated

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ports a remarkable case of unilateral hypertrophy of the male breast. The female breast is affected more often. When an entire extremity is affected it may show uniform hypertrophy or one or more digits may be the seat of enormous grotesque overgrowth out of all proportion to the rest of the limb. This is especially true of the great toe. With involvement of the trunk the viscera of the affected side may be hypertrophied. Harwood reports a case with pubertas precox and an abdominal tumor believed to be suprarenal in origin. With involvement of the tongue there may be difficulty in swallowing and talking.

About 20 % of the reported cases of hemihypertrophy have been feeble minded in varying degrees. Scott states that in some cases on the affected side the sebaceous glands seem to have an abnormal secretion, the sweat glands may be abnormally active, the hair more profuse, the nails grow faster and the teeth erupt earlier. In facial involvement precocious dentition may be striking. Leri and Sartre report the case of a girl with right facial hemihypertrophy who at the age of 2½ years shed her right lower median incisor and four months later her right lower lateral incisor. These were replaced promptly by permanent teeth while the corresponding deciduous teeth on the normal left side remained at the time of examination when she was 5 years and 10 months old. Also at the age of 3 years *she had her right upper and lower six year molars.* Dentition on the right side was 3½ years ahead of that on the left as judged by normal standards.

Wakefield and Hines report a number of congenital abnormalities in association with hemihypertrophy including hypospadias, cryptorchidism, polydactylism and congenital heart disease. Strickler reports a case of complete hemihypertrophy in a 48 year old man who showed erosion of the sella turcica. A year and a half later without treatment there was no further erosion of the sella. He showed marked defect in his visual fields and it was felt that he had a complicating pituitary tumor.

Extensive laboratory studies have been negative. Cohen reports a case with excessive glucose tolerance showing no glycosuria after 650 grams of glucose.

Diagnosis. — *Edematous enlargement* of a part of the body due to vascular occlusion or stasis is excluded readily. Hemihypertrophy must be distinguished from *hemiatrophy* by considering whether the smaller or the larger side of the part of the body involved is the normal one. As stated in the discussion of hemiatrophy, often it is helpful to exclude one half of the patient's body from the examiner's view and look at one half at a time. With bony involvement x-ray will show abnormally large bone shadows in hemihypertrophy and abnormally small ones in hemiatrophy.

in the literature prior to 1914 but beginning with that year the number has grown rapidly

Etiology — This is unknown Various hypotheses have been advanced such as vascular obstruction especially in the embryo incomplete unilateral paralysis of vasomotor nerves some substance in excess on one side of the body that is activated by a hypophyseal secretion (!) an incomplete process of twinning (Gesell) unilateral maldevelopment of the vascular system (Chandler) overgrowth of the anlagen on one side of the embryo (this explains nothing), etc but none of these have been proved Chandler discusses overgrowths of various parts of the body in a broad way making no essential distinction between a single large toe e g and hemihypertrophy viewing them all as local overgrowths While the vast majority of cases appear to be congenital a few have been reported that seemed to have a post natal onset usually in infancy or childhood Both sexes are affected but the female somewhat more commonly The right side is affected nearly twice as often as the left Syphilis is not a factor

Incidence — In 1933 Wakefield and Hines stated that in 1926 there were 195 case reports of hemihypertrophy listed in the Surgeon General s library 44 of which were total They found 28 more cases of total hemihypertrophy reported between 1926 and 1933 To these they added 8 cases of their own making in all 80 cases of total hemihypertrophy reported up to that time We may safely state that over 100 total cases have now been reported A familial incidence is extremely rare but Reed reports a brother and sister not twins who were affected

Pathology — That portion of the pathology which is obvious on ordinary clinical methods of observation will be discussed under Symptomatology The most significant thing is the widespread deposit of fat in the soft tissues and also in the bones when they are involved The marrow cavities and even the Haversian canals may contain enormous numbers of fat cells The cortex of the bone is thinned Leri reports a case with epileptic attacks in which necropsy showed the dura to be adherent to bony enlargements that showed externally

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About 20% of the reported cases of hemihypertrophy have been feeble-minded in varying degrees. Scott states that in some cases on the affected side the sebaceous glands seem to have an abnormal secretion, the sweat glands may be abnormally active, the hair more profuse, the nails grow faster and the teeth erupt earlier. In facial involvement precocious dentition may be striking. Leri and Sartre report the case of a girl with right facial hemihypertrophy who at the age of ⅔ years shed her right lower median incisor and four months later her right lower lateral incisor. These were replaced promptly by permanent teeth while the corresponding deciduous teeth on the normal left side remained at the time of examination when she was 5 years and 10 months old. Also at the age of 3 years she had her right upper and lower six year molar. Dentition on the right side was 3½ years ahead of that on the left as judged by normal standards.

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Etiology — This is unknown Various hypotheses have been advanced such as vascular obstruction especially in the embryo incomplete unilateral paralysis of vasomotor nerves some substance in excess on one side of the body that is activated by a hypophyseal secretion (?) an incomplete process of twinning (Gesell) unilateral maldevelopment of the vascular system (Chandler) overgrowth of the anlagen on one side of the embryo (this explains nothing) etc but none of these have been proved Chandler discusses overgrowths of various parts of the body in a broad way making no essential distinction between a single large toe e g and hemihypertrophy viewing them all as local overgrowths While the vast majority of cases appear to be congenital a few have been reported that seemed to have a post natal onset usually in infancy or childhood Both sexes are affected but the female somewhat more commonly The right side is affected nearly twice as often as the left Syphilis is not a factor

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such case in a young man who had had one testis destroyed and who had developed sexual dysfunction with a feminine build before the erythrocyanosis appeared In most cases the condition is present only in cold weather and in those in which it remains throughout the year it is much worse in the cold season Juster has noted it in certain hemiplegics having marked sympathetic disturbances involving only the affected side and in certain cases of poliomyelitis or myelitis with involvement of the medullary sympathetic centers revealed by disturbances in the vasomotor mechanisms and temperature of the affected limb He therefore concludes that the condition is due to an endocrine dysfunction chiefly ovarian but also to some degree thyroid and hypophyseal with resulting disturbance of the sympathetic nervous system which is aggravated by exposure to cold and circulatory stasis Oldham noted that the cyanosis disappeared under spinal anesthesia Women and notably adolescent girls because of the prevailing fashions of short skirts and sheer hosiery have their legs especially exposed to cold This probably explains the paucity of reports of cases before such fashions came in vogue The condition has been found associated with polyarthritic gonorrhea tuberculosis syphilis focal infection and constipation but contrary to earlier views that attributed it to a tuberculotoxin to syphilis or to focal infection there is no evidence that such factors play any part in the etiology

Pathology —The pathology which is obvious on ordinary inspection will be described under Symptomatology Under a hand lens with the patient standing the affected areas show deeply colored projections with a less deep color in between them presenting especially in long standing cases a fine lacework of little capillaries and venules The skin is stippled with small reddish spots and in the center of each spot is a keratinized focus These spots are enlarged and pigmented hair follicles the keratosis pilaris of the French It is especially the venous loops of the capillaries in the papillae that are affected showing minute so called aneurisms The diameter of these varies with vasomotor changes Kistiakovsky considers erythrocyanosis as identical with acrocyanosis but most authorities disagree with this view When subcutaneous nodules form they contain giant cells according to Telford and Simmons but are not of true tuberculous type

Symptomatology —The condition usually occurs in young girls with a florid complexion large reddish arms and thick strong legs which are hairy except for their lower portions The patients indeed may give the appearance of health and strength above the average When standing they show above the malleoli more or less symmetrical diffuse areas

with vague boundaries which may extend over the whole lower part of the legs of a violaceous reddish color on a cold clammy infiltrated skin On assuming a posture with the legs stretched out horizontally on a level with the pelvis this supramalleolar cyanosis disappears or diminishes greatly Usually the patient notes that on getting up in the morning her legs are of normal color or only slightly reddish violet but by evening the discoloration is marked and they feel swollen heavy and perhaps a little painful Often her chief complaint is a cosmetic one viz that the discolored areas are unpleasantly conspicuous through sheer hosiery

Strong digital pressure will produce a brief period of pallor in the compressed tissue followed by a return of the original color which Telford and Simmons liken to the flowing of a subcutaneous lake of ink or according to Juster a red color replaces the pallor and remains in sharp distinction to the bluer color of those portions of the lesion that have not been compressed for from several minutes to an hour before regaining its original hue The discoloration may or may not encircle completely the lower part of the leg It tends to be more marked on the posterior and outer aspects In rare cases especially when tight garters constrict the affected area may extend up to the garter line The infiltration consists of a firm swelling of the skin and subcutaneous tissues which usually feels objectively cold and which does not pit on pressure The infiltrated areas usually are hairless though the legs above them as a rule are conspicuously hairy Painful and very tender nodosities from 1 to 2 cm in diameter may be present and these tend to resolve very slowly and may leave subcutaneous scars In the absence of chilblains which may be associated they do not rupture or ulcerate Some patients can forecast the appearance of these nodules from severe itching which may precede them

When the lesions depend on some unilateral neurological condition such as a hemiplegia unilateral paralysis from poliomyelitis etc they appear only on the affected side Irregular or excessive menstruation often accompanies erythrocyanosis In a severe case the infiltrated area in a leg may resemble a cuff starting just above the malleoli and shading off higher up causing a clumsy and obvious deformity The sensation of coldness in the legs and intolerable itching and burning pain may keep the patient from working Telford and Simmons note that the thin spare leg seems immune to the disease Juster notes that there may be associated acrocyanosis of the hands hypogenital hands chilliness nonchalance emotionalism fatty deposits about the hip and shoulders hyperhidrosis especially of the extremities hypertrichosis of the body and upper lip and a tendency to ecchymoses and other types of hemorrhages Occasionally

erythrocyanotic areas are found on the backs of the elbows similar to those on the legs and very rarely according to Kistiakovsky the loins buttocks wrists shoulders or face may be involved Sometimes an unaffected sister will complain about discomfort in bed at night from the cold legs of the affected sister

Diagnosis — *Erythema induratum* (Bazin s disease) a form of tuberculosis of the skin may resemble erythrocyanosis closely but it begins as subcutaneous nodules which eventually ulcerate and does not show the relation to cold and posture especially the former which characterizes erythrocyanosis *Erythema nodosum* may be suggested but the nodules of that condition usually are scattered more widely over the lower extremities are redder and less bluish than the lesions of erythrocyanosis and the fever and joint symptoms which occur are lacking in erythrocyanosis *Erythromelalgia* affects the foot more than the leg causes far more pain often in crises is redder and is made worse by heat and relieved by cold

Acrocyanosis has a different location affecting especially the fingers and toes and the tips of the ears and nose and lacks the infiltration and nodules of erythrocyanosis For a further discussion of acrocyanosis see Vol II Chap XIV Faicon Vasilesco and Bruch point out that the *acroerythrosis of Bechterew* shows a redness but no cyanosis but they add that various conditions may represent variations in the vessels affected involvement of the capillaries producing erythema of the venules cyanosis and of the arterioles if paralytic redness or if spastic pallor

Prognosis — Minor degrees of the condition are very common and trivial but as noted above severe cases may be disabling With proper treatment however recovery from the latter or very marked and apparently permanent improvement is the rule

Prophylaxis — This depends on proper protection of the legs by clothing While fashion decrees short skirts and thin stockings the physician rarely will be able to prevent this disease despite the availability of simple adequate means Tight constricting garters should be avoided

Treatment — Mild cases require little or no treatment Proper protection by clothing in cold weather is indicated but the patient rarely will consent to this Tight circular garters should be discarded in favor of some non constricting support Periods of rest in a warm bed with the legs horizontal or elevated are indicated for those who can afford such Endocrine treatment may be tried for menstrual disturbances as described in Vol III Chap XVIII Parkes Weber suggests calcium For severe disabling cases such methods are of little use but here lumbar sympathectomy bilateral lumbar cord ganglionectomy offers hope of cure or

very great improvement Oldham noted that after operation for the first few days the skin over the swellings was bright red but the color then returned to normal and remained so in his case 1½ years later The swellings persisted but did not increase further Telford and Simmons report another case in which after operation the cuff like swellings in the legs diminished to about one fourth their previous size They record another patient as being well four years after operation and report no failures in 10 cases

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PROGRESSIVE PALLIDAL DEGENERATION

Definition — A rare familial disease often beginning with progressive *blindness in early childhood due to retinitis pigmentosa and developing* some years later a progressive muscular rigidity without tremor and without evidence of pyramidal tract disease

History — In December 1924 at a meeting of the Philadelphia Neurological Society F X Dercum presented two brothers suffering from this

condition The elder gave a history of dim vision appearing at the age of 3 or 4 years This was found to be due to retinitis pigmentosa By the time he was 12 he was sent to a school for the blind At the age of 14 his lower extremities were stiff At 18 he was helpless and dysarthric There were no pyramidal signs and no tremors He died about 3 years after Dercum s discussion death being preceded by intense rigidity The younger brother also showed retinitis pigmentosa and an earlier stage of extrapyramidal rigidity In 1932 Winkelman published a paper on the condition and gave it its present name

Etiology and Pathology —The etiology is not known The disease affects essentially the pallidum and the reticular portion of the substantia nigra Winkelman calls these two structures together the pallidal system According to Keschner the ganglion cells in this system are destroyed and replaced by lipoid material and iron containing pigment Cirrhosis of the liver is absent

Symptomatology and Diagnosis —When retinitis pigmentosa is associated the first symptom is progressive bilateral blindness appearing in early childhood Several years later extrapyramidal rigidity sets in usually appearing first in the lower extremities and progressing in both extent and degree until extreme general bodily rigidity results and the patient becomes completely helpless

The absence of tremor differentiates this condition from *parkinsonism* and the lack of mental symptoms involuntary movements and evidence of cirrhosis of the liver from *progressive hepatolenticular degeneration* Blindness due to retinitis pigmentosa is of course not characteristically associated with either of the two latter conditions

Prognosis — The disease is progressive and incurable Death usually results from intercurrent infection

Treatment —No treatment is known that will stay the progress of the disease Stramonium atropine, syntropan cobra venom etc may be tried in an effort to lessen the degree of the rigidity as they are tried in parkinsonism Stramonium atropine and drugs of like action must be given to the point of mild toxicity to be effective as a rule Syntropan according to Alpers in a discussion of parkinsonism before the Guilford County (N C) Medical Society in September 1939 seems to be relatively free from the undesirable side actions of atropine and stramonium especially upon the eyes and bladder The chief objection to it is its rather high cost Alpers states that from 400 to 600 mg is the usual effective dose four such doses being given daily The patient should be watched for the usual signs of toxicity in drugs of the atropine series and the dosage regulated accordingly

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Cerebellar Agenesis

Definition — Failure of development of a part or all of the cerebellum

History — According to Baker and Graves Combette gave the first report of a case of complete absence of the cerebellum in 1831 This was in an epileptic idiot Dorothy Priestley described another case of total absence in 1920 Baker and Graves state that Ferrier in 1866 reported the case of a feeble minded girl aged 15 whose cerebellum was represented by a minute nodule the pons and cerebellar peduncles being absent Solovtzoff reported a case of complete absence of the vermis in 1901 In 1853 Salter reported a 44 year old male epileptic with a large internal hydrocephalus and complete absence of the left cerebellar hemisphere vermis and left peduncles The space usually occupied by the cerebellum was occupied by the cerebrum so we may assume the tentorium was absent on the left side Marked curvature of the spine was present also In 1876 Leyden reported a case with a very minute cerebellum associated with meningocele and syringomyelia Cornelius in 1907 collected several cases of unilateral cerebellar defects associated with contralateral cerebral defects In 1898 Neuberger and Edinger reported a case in a man aged 46 showing absence of the greater part of the right cerebellar hemisphere Strong published an excellent pathological discussion of the subject in 1915

Etiology — This is unknown

Pathology — This varies with the part or extent of the cerebellum affected Other parts of the brain may be involved also The main defects in several cases have been noted already in the historical section Strong found the following structures markedly defective most of the left cerebellar hemisphere possibly a part of the vermis and left superior colliculus the right inferior olivary nuclei the right central tegmental tract the left corpus restiforme the left middle cerebellar peduncle the right pons nuclei the right pes and substantia nigra the left nucleus dentatus the left superior cerebellar peduncle and the right red nucleus Involvement of the extracerebellar structures apparently was due to the lack of the

normal cerebellar connections with them Baker and Graves first case showed the cerebellum almost entirely absent The medulla showed bilateral absence of the olives and extreme width of the rhomboid fossa The lateral ventricles were normal In their second case the left hemisphere was greatly diminished and the vermis absent In Davison s case there was complete absence of the cerebellum with a poorly developed pontobulbar system

Symptomatology and Diagnosis — This will depend of course on the extent of the cerebellar agenesis and on what other parts of the brain may be affected Typically the usual cerebellar symptoms ataxia asynergia dysmetria etc are present if and when the child becomes old enough to manifest them and are noticeable from the earliest age at which it is possible to detect them

The patient whose brain was examined by Strong was a girl aged 3 years and 4½ months She was small for her age and had a noticeably small head She was very weak and unsteady in all her movements and sat almost all day in a high backed chair She could walk but with very uncertain gait staggering to one side and she held fast to chairs and other objects in getting about She was unsteady also in grasping a proffered object She could move her head but the movements were slow No paralysis was noted There was marked bilateral nystagmus the exact type not being noted She was mentally dull and took no interest in toys etc She talked poorly and indistinctly with scarcely any formed sentences There were no convulsions or spasms There was no vomiting until her last illness (measles and bronchopneumonia) For weeks she cried and rolled her head from side to side After crying she would hum a popular air and accompanying this she rotated her head from side to side usually in time with the music and eventually rubbed all the hair off the back of her head

Priestley s patient was a wasted female infant aged 4 months the second child of healthy parents and a full term baby She had hydrocephalus with exophthalmos and spina bifida Her extremities were spastic and her head retracted Her pupils reacted to light She died of bronchopneumonia The cerebellum and pons were completely absent In Salter s case already mentioned the epileptic attacks were ushered in by severe pains in the head

Baker and Graves first patient a boy could not walk till he was 4 years old and then often fell He got worse He was a low grade imbecile and had to be fed He was unwilling to stand though he could do so He walked with his legs partly doubled but never crawled When sitting he would slump forward He always slept doubled up He

could hold his head erect He carried his arms partly flexed He died at 19 of gastroenteritis Baker and Graves obtained no clinical history from their second patient merely studying the brain pathologically

The *differential diagnosis* from the more common progressive cerebellar ataxias in childhood may be impossible though usually the latter develop more slowly and insidiously The difficulty lies in the fact that cerebellar symptoms can be detected only as the child develops enough to make them evident If other developmental defects such as spina bifida hydrocephalus etc are present also the diagnosis is suggested

Prognosis —There is obviously no hope for improvement in such a developmental defect Intercurrent infection usually closes the scene

Treatment is of no avail

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THE MARKUS ADIE SYNDROME

Synonyms —Adie s syndrome Markus syndrome

Definition —A benign non syphilitic syndrome characterized in its typical form by a pupil which resembles the Argyll Robertson pupil in

some respects yet differs from it in certain essentials and by absence of the patellar and Achilles tendon reflexes without discernible effect on the general health Rarely the tendon reflexes may be absent in the upper extremities with or without their absence in the lower The condition while relatively rare is of great importance to the practitioner because of the case with which he may fall into the disastrous error of confusing it with tabes dorsalis and thereby subjecting patients affected with it to prolonged expensive and unjustified treatment to say nothing of the mental suffering to the patient associated with the diagnosis of tabes

History — In 1902 three men working independently described what has come to be known as the myotonic pupil or pupillotonia in non syphilitics and differentiated it from the Argyll Robertson pupil These men were Saenger Strassburger and Nonne One of Nonne s patients also had a loss of Achilles reflexes but as he also had diabetes the lost reflexes were attributed to that disease

In 1906 Markus reported three cases showing the myotonic pupil One of these patients a physician had normal patellar reflexes It is interesting to note that twenty seven and a half years later Weber re ported that this patient remained in excellent general health and was doing active scientific work In another case that of a young woman no statement was made regarding the tendon reflexes The remaining patient however the first of the three reported a 12 year old boy had a complete absence of the patellar and Achilles reflexes This seems to be the earliest record in the literature of the typical syndrome Of special interest in this case is the fact that twenty seven and a half years later Weber presented this same patient before the Royal College of Physicians of London and demonstrated certain changes in his condition to be noted later

In 1921 Behr gave a very full discussion of the myotonic pupil Jel liffe in the same year noted its occurrence in connection with hypothy roidism A number of other articles appeared on the subject during the next decade In 1931–2 Adie published his classic papers and pre ented such a clear definite clinical picture that his name has been associated with the syndrome ever since One of the most recent publications on the subject is that of Heersema and Moersch of the Mayo Clinic

Etiology and Pathogenesis — This is unknown About 80 per cent of the cases have been in females Children are affected Syphilis is not a factor Chavany suspects it to be an unknown disturbance of the vegetative nervous system Foster Kennedy speculates on the question as to what part of the nervous system could be involved and produce both pupillary changes and loss of the knee and ankle jerks and suspect

the hypothalamus because of its far flung connections Dressler reported Adie's syndrome associated with hippus in three sisters an unusual familial occurrence Inman postulates emotional causes in some instances at least and cites a case in which the left eye apparently became affected while the patient was purchasing a wreath for her father's funeral The condition being entirely benign no necropsy studies have been reported

Symptomatology and Diagnosis — In the typical form the symptoms consist of the peculiar pupillotonia and absence of the patellar and Achilles reflexes in the absence of any evidence of syphilis or any other neurologic disease Very rarely as mentioned above the tendon reflexes may be lost in the upper extremities The loss of tendon reflexes is almost always bilateral but the pupillotonia is unilateral in about 70 to 75 per cent of the cases Either eye may be affected It is of great importance to distinguish the myotonic pupil from the Argyll Robertson pupil Both Moore and Adie have given important differential diagnostic points They are summarized in the following table

Argyll Robertson Pupil	*Myotonic Pupil*
Usually bilateral	Usually unilateral
Definitely miotic	Usually larger than normal
No reaction to light	Ordinary light reaction absent but may react slightly and slowly to very strong light also dilates slowly in the dark and returns slowly to original size on returning into ordinary light
Accommodation convergence reflex prompt	Accommodation-convergence reflex usually very slow
Ciliospinal reflex absent	Cilio pinal reaction slight when pupil contracted
Response to atropine poor — only partial mydriasis	Re ponse to atropine normal
Response to eserine — pupil already miotic	Response to eserine normal
Other evidences of syphilis	No evidence of syphilis

By reaction to light is meant both the direct and consensual light reflex

Adie emphasizes the all important point that a pupil which reacts to accommodation but not to light is not a true Argyll Robertson pupil unless the other criteria mentioned above are present also and that such a pupil may be found in many conditions including non syphilitic congenital

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CHAPTER XLIV

ANHIDROTIC SYNDROMES

By FREDERICK R. TAYLOR AND DAVID CAYER

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Acquired Anhidrosis with Circulatory Insufficiency

Synonym.—Fog's syndrome.

Definition.—An acquired inability to sweat with circulatory insufficiency due to extreme vascular dilatation in the skin.

History.—In 1936 Mogens Fog of Copenhagen reported such a case, apparently unique in the literature at that time.

Etiology and Pathology

This condition developed in a previously well young man of normal appearance after a prolonged illness of paratyphoid fever The family history was free of sweat disturbances ectodermal dysplasia or metabolic abnormalities Histological study of the skin after the condition had lasted six years showed about half of the sweat ducts to be abnormal cystic and lined with very flat cells This suggests that the disturbance was chiefly in the innervation of the sweat ducts and not solely a diseased condition of the skin itself One case observed by the senior author (F R I) was complicated by, or was due to, disseminated sclerosis

Symptoms

Having sweated normally before and during prolonged paratyphoid fever this young man never sweated thereafter Subsequently, when he walked rapidly or engaged in manual labor, especially out in the sun shine he soon felt indisposed, his skin, especially that of his face, felt overheated, he had dull precordial pain, palpitation, dyspnea and often painful paresthesias of the face and extremities These symptoms might last as long as an hour and leave him exhausted and unable to resume work Physical examination was negative except for a dry scaly skin There was no demonstrable neurological disturbance Numerous laboratory examinations were negative Urine output was increased, averaging about 2 000 c c per 24 hours

Artificial hyperthermia was tried to see its effect, after 19 minutes it was discontinued, because he was exceedingly ill with dyspnea, small weak and rapid pulse and rales at the bases of his lungs, his skin was scarlet, but devoid of sweat Body temperature was normal with normal rhythmic fluctuations

Extensive tests indicated that there was nothing wrong with heat regulation under normal demand lack of skin evaporation being compensated by increased conduction and radiation If demand for the latter were increased compensation could be brought about only at the expense of marked peripheral vascular dilatation enough to cause evidences of circulatory insufficiency as expressed by the symptoms already described

In 1945 Engelhardt and Melvin reported another case in a 49 year old woman In her youth she had typhoid fever Subsequently she had

several uneventful pregnancies Thirteen years before the authors saw her, i e at the age of 53 she felt nervous, short of breath, hot and while scrubbing the kitchen floor was seized with burning of the skin and fever Thereafter she had frequent episodes of itching and burning of the skin, accompanied by fever which sometimes rose to 10[illegible] F This always occurred in a hot environment and was in proportion to the external heat Frequent cold baths gave great relief On admission to the Charity Hospital in New Orleans (Tulane Medical Service) on July 15 1943 her temperature was 99 F pulse 80 blood pressure 1[illegible]0/80 There was marked wrinkling of the skin especially on her face The thyroid was questionably enlarged but her basal metabolism was reported normal Serological and other laboratory tests were normal

Prolonged investigation established inability to sweat and a direct and proportionate relation between the height of the patient s fever and the excess of environmental heat Repeated biopsies from various parts of the skin showed a generalized atrophy of the sweat glands There was no family history of anhidrosis

Two years later there was no improvement

Hysterical anhidrosis such as Berkman and Horton reported is not permanent and sweating is caused by pilocarpine It should not be confused with this condition

Treatment

Occupations requiring relatively little physical exertion give no particular discomfort Frequent cold baths are useful when the patient is in a hot environment

HEREDITARY ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE

Definition—An hereditary condition in which there is a lack of proper development of certain ectodermal structures notably the skin hair and teeth The chief clinical manifestations are an intolerance to heat absence of sweating and defective dentition Other parts of the body also may be affected in specific individuals or groups

History

According to Thannhauser Widderburn in 1838 described 10 cases in a Hindu family showing total absence of sweating deficient hair

(scalp, axillary and pubic) and partial or complete absence of the teeth Thadani makes it seem likely that anhidrotic ectodermal dysplasia is relative common in India in the cases of the "Bhudas of India, a toothless type of man", who does not perspire In 1848 Thurnam described two cases showing an associated absence of the lacrimal glands apparently a unique observation in the literature of the subject In 1883 Guilford an American dentist described a patient with the disease who was totally edentulous He also noticed the existence of a "saddle" nose In 1886 Jonathan Hutchinson reported a case showing an associated absence of the nipples In 1929 Weech gave the condition the name by which it is now known Cases have been reported at all ages from infancy to the sixth decade The oldest case was aged 58 The syndrome of anhidrosis with hypotrichosis and anodontia is observed most frequently in the Anglo-Saxon race Cases have been reported from India Russia Germany, Sweden France, England, United States Australia and Portugal The disease is rare in its complete form although numerous cases of multiple ectodermal defects have been reported Clouston alone reported 119 cases in six generations of one family having defective hair and teeth without absence of sweat glands Helweg-Larsen and K Ludvigsen describe a Swedish family in which 14 of the members showed congenital anhidrosis A few very scattered sweat points were present where single hypertropic, sweat glands were demonstrated by skin biopsy Neurolabyrinthitis appeared in these patients between the ages of 35 and 45 years There were however no dental defects cranial deformities defective growth of hair, ozena or other associated features of hereditary ectodermal dysplasia

Etiology

Beyond the fact that the condition is an hereditary defect, little is known The characteristic inheritance of hereditary ectodermal dysplasia of the anhidrotic type is predominantly but not strictly sex linked Weech believed that mutations in the genes of any individual may occur regardless of sex Thus both sexes may be affected He believes that this condition as well as other ectodermal anomalies may arise as a result of a genetic mutation which occurs not by accident but as the occasional expression of a suppressed tendency to change inherent in the make up of the genes themselves DeSilva concludes that it is an hereditary condition due to a gene mutation in the x chromosome and that it is sex linked and not completely recessive

An endocrine origin has been suggested, but nothing constant has been observed to point to any specific endocrine etiology Occasional cases seem to give some credence to this view as for example Thannhauser's patient whose symptoms suggested adrenal medulla insufficiency This is an interesting speculation however since among the tissues derived from the primitive ectoderm is the nervous system including the adrenal medulla and the anterior lobe of the pituitary gland

The dry skin is due to a lack of development of the sweat glands and has no relation to myxedema Syphilis is not a factor as apparently no case yet has been reported that has shown any positive laboratory tests for that disease The male sex predominates The condition is present at birth becomes obvious in infancy and since the patients are otherwise healthy and live to a normal age may be found in middle life or beyond

Cole reports a defect of hair and teeth in cattle probably hereditary

Pathology

The gross structural changes will be noted under symptomatology Structural abnormalities may be noted in any or all of the tissues derived from the primitive ectoderm These are 1) the nervous system including the adrenal medulla) the epidermis 3) the lining cells of the sebaceous sudoriferous and mammary glands 4) the hair and nails 5) the epithelial lining of the nose sinuses cheeks roof of the mouth and the epithelium of the cornea conjunctiva and lacrimal glands 6) the enamel of the teeth 7) the anterior lobe of the pituitary gland and 8) the neuroepithelium of the sense organs The main pathological change is the absence of sweat glands Mogens Fog in his patient cited in the preceding subsection found the sweat glands to be merely cystic hollows covered with cells

Histologically skin biopsies have shown complete or nearly complete absence of sweat and sebaceous glands and of hair follicles X ray examination of the jaw usually reveals a partial or complete absence of tooth buds The aplasia of the dental structure may be one of total anodontia with complete absence of both deciduous and permanent dentition or partial anodontia with absence of one of more of either the deciduous or permanent dentition but with the presence of teeth

Few abnormalities have been reported in the central nervous system The basal metabolism usually has been found to be within normal limits

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The clinical characteristics of the disorder may be summed up as follows The general development and nutrition usually are good The hair on the scalp and in the axillary and pubic regions is fine, dry, sparse and lanugo like Frequently it may be pulled out without pain or breaking The eyebrows usually are totally absent and eyelashes are scanty or absent Curiously enough the mustache and beard of some adult males have been well developed as in the case of Tendlau's Thannhauser however reports a lack of secondary sex hairs in his patient a 23 year old man The thin glossy smooth dry parchment like skin is one of the most remarkable features of the disease It often feels abnormally warm to the touch and shows marked hypersensitivity In a number of cases various eruptions have been described such as milium xeroderma pigmentosa large superficial degenerated sebaceous glands with hyperkeratosis dilated follicular orifices with surrounding acanthosis etc Allergic phenomena and cutaneous sensitivity are frequent The specific sensory endings in the skin may be defective also Thannhauser reports pigmentation associated with low blood pressure suggestive of Addison's disease The nails usually are normal but flat or even concave spoon shaped nails have been noted Rarely the nipples and the lacrimal and mammary glands have been defective or absent Absence of the lacrimal glands with resulting distressing xerophthalmia was noted in Thurnam's two patients Atrophic rhinitis with ozena is a frequent occurrence and is characterized by a putrid odor the formation of crusts atrophy of the mucous membrane and spaciousness of the nasal cavity Depression of the nasal bridge is accompanied by prominence of the supraorbital ridges The teeth may be absent or pegged or even tusk like Often teeth which do appear decay and fall out prematurely or are widely separated from one another X rays may or may not reveal additional unerupted teeth The lips may be thick and protrusive and may lack a well defined vermilion border Several authors have reported an unusually long tongue as a feature of the disorder Guilford's patient a 48 year old man had no sense of smell and was almost devoid of a sense of taste He employed a box in hot weather to pour water over his clothing as soon as it became dry Dysphagia may be present due to dry mucous membranes and scanty saliva and the mucous membrane abnormality may produce voice changes hoarseness or even complete aphonia

No gross malformations of the nervous system have been noted although a few patients have shown some mental deficiency Halpern

although Weech reported one case showing rates of +59, +37 and +9 per cent on three tests. His other patient showed a basal metabolic rate of −10 per cent.

No remarkable changes have been noted in the blood chemistry except in Thannhauser's patient, who had a low fasting blood sugar and a flat sugar tolerance curve. Lowenburg and Grimes report a patient showing decreased sulphur content of the nails and a high sugar tolerance. Blood calcium and phosphorus studies, when done, have been reported to be normal. Some disturbances in the blood forming tissues were reported by Marques who found a neutropenia with lymphocytosis and a decrease in the blood platelets.

Goeckermann states that the heat regulating mechanism is affected by the inability to sweat and Tendlau that the body temperature was not lowered by prolonged cold baths. Hiebert and Garland using Talbot's technique, noted that the skin temperatures on the face, trunk and extremities of their patient who had a normal rectal temperature equalled those of other children with a rectal temperature of 40° C (104.5° F). They recorded the skin temperatures as follows

	Patient (° C)	Standard (° C)
Face	35.2	33.[illegible]
Trunk	37.1	35.5
Extremities	37.8	33.0

The urine and other blood studies have been reported normal and the Mantoux tuberculin test negative.

Symptoms and Clinical Features

Most of these patients come to physicians because of marked intolerance to heat or unexplained extreme hyperpyrexia. The sole inadequate physiological function is the failure to radiate sufficient heat when subjected to a hot atmosphere or following vigorous exercise. This is the result of a defect of the lining of the sudoriferous glands with absence of sweating. It is more common in summer but may occur in winter from wearing too heavy clothing. It may occur abruptly, particularly in infants, who are too heavily covered during hot weather. It is possible that many of these infants die with rhinitis, otitis media, pneumonia and hyperpyrexia before the distinctive dentition has occurred and before they are old enough to complain of heat or the true condition is suspected.

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Symptoms and Clinical Features

Most of these patients come to physicians because of marked intolerance to heat or unexplained extreme hyperpyrexia The sole inadequate physiological function is the failure to radiate sufficient heat when subjected to a hot atmosphere or following vigorous exercise This is the result of a defect of the lining of the sudoriferous glands with absence of sweating It is more common in summer but may occur in winter from wearing too heavy clothing It may occur abruptly, particularly in infants who are too heavily covered during hot weather It is possible that many of these infants die with rhinitis otitis media pneumonia and hyperpyrexia before the distinctive dentition has occurred and before they are old enough to complain of heat or the true condition is suspected

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and Curtis have suggested that the gene responsible for the dysplasia has a depressing influence on mentality Most of the reported cases, however, have shown a normal mentality Other congenital malformations apparently unrelated to the syndrome, such as cardiac defects, malformations of the external ear, polydactylism and spina bifida are observed sometimes in these patients

Diagnosis, Prognosis and Treatment

Congenital syphilis must be excluded by appropriate laboratory and clinical data A positive Wassermann reaction or a family history of syphilis has not been found in any of the cases thus far The only common feature of both conditions is the saddle nose The deformity of the nose is not specific and can hardly be used as a diagnostic criterion without other manifestations Chondrodystrophy, trauma in infancy and other conditions may result in a similar deformity The radiating wrinkles about the mouth of the patient with dysplasia are due to the absence of tissue and can be distinguished from the true rhagades of congenital syphilis which are due to linear ulceration and scar tissue The other findings of mulberry molars, interstitial keratitis and osteoperiostitis particularly of the tibias in syphilis, and the absence of response of ectodermal dysplasia to antisyphilitic therapy lead to a correct diagnosis Hypopituitarism can be ruled out easily by the routine examination Progeria shows neither so dry a skin nor the dental defects and arteriosclerosis and renal changes usually are present, even in infancy In progeria the lips are thin the tongue is short and small sweating is normal and dwarfism is marked, temperature is normal or subnormal

The condition obviously is permanent and incurable Patients with the disease should live in a cool moist climate Dental aid for the fitting of artificial dentures should be sought Clouston found that the ozena in his cases responded to the use of estrogenic substances

Exhaustion Anhidrosis

Synonym—Thermogenic anhidrosis

Definition—A failure of the sweat mechanism with temporary functional anhidrosis

Etiology

Shakravarti and Tyagi attributed the etiology in their case to a lesion in the hypothalamic region or in the descending fibers of the sub thalamic nucleus Wolkin however, felt that it was unlikely that failure of the sweat mechanism was due to a central or thermoregulatory center disturbance in the hypothalamus since sweating of the face and neck persisted in his patients As there is no evidence that the face and neck have a separate control center he reasoned that the disturbance was peripheral He suggested that an initial hyperhidrosis overtaxed the thermoregulatory mechanism to the extent of producing a temporary functional paralysis

It is apparently unrelated to humidity cases having been observed in persons exposed to desert heat as well as those in the hot highly humid climate of the South Pacific

Symptoms and Clinical Features

The symptoms come on during exposure to excessive heat and sun light either with or without physical exertion The onset usually is associated with or preceded by cessation of sweating This in turn usually is preceded by a distinct period of profuse hyperhidrosis of several days to several weeks duration In the case described by Shakravarti and Tyagi a 46 year old Anglo Indian engine driver had absence of perspiration on the left side of his body which occurred in 1935 1938 and 1939 Each episode followed a period of service as a train engine driver

The 8 patients reported by Wolkin as well as the 2 reported by Novy and Ramsey showed a spectacular loss of sweating uniformly limited to the body region below the neck in pronounced contrast to the outpouring of sweat from the face and neck The axillary and inguinal regions were perfectly dry The skin of the entire body below the level of the neck showed a diffuse papular eruption each papule being the size of a large pin head giving the appearance of goose flesh In the cases of longer duration a fine branny desquamation appeared

Diagnosis

This syndrome must be differentiated from heat stroke and heat exhaustion The former is characterized by collapse delirium irritability

visual disturbances and occasionally, nausea and vomiting. The significant physical findings in addition to the altered mental state, include the hot dry skin, elevation of body temperature, tachycardia and increased depth of respiration.

In heat exhaustion symptoms usually are manifested by headache, loss of appetite, drowsiness, weakness, visual disturbances, vomiting, vertigo, inability to walk, as well as by cramps in the limbs and abdomen. Physical examination of these persons shows the skin to be cold and clammy with diffuse perspiration. The mouth temperature is normal, the pupils dilated, the pulse increased and the blood pressure lowered.

In exhaustion anhidrosis the typical history of rather sudden onset of generalized weakness, subjective warmth and discomfort, dizziness, headache and shakiness usually preceded by a period of excessive sweating and the diffuse uniform appearance of "goose flesh" over the sharply demarcated area of anhidrosis usually makes the diagnosis. The patients described also had pronounced hyperhidrosis of the face and neck. Their response to cholinergic drugs (pilocarpine and mecholyl) paralleled the response to heat.

On trial exposure to sunlight following hospitalization the initial symptoms were reproduced. After recovery of the sweating function, however, the symptoms could not be produced even when the patients were again temporarily subjected to excessive heat.

Treatment

The mere removal of these patients from excessive heat rapidly allays the symptoms. All of the patients improve promptly with a cool environment and rest. It is important to recognize that these patients require an avoidance of exposure to excessive heat until the sweating function has returned to normal. Salt is not indicated and is of no value. As the condition improves, the skin eruption disappears, and the skin resumes its normal appearance.

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